

ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY

VOL. 58

DECEMBER, 1949

No. 4

LXXXIII

RADIUM THERAPY IN PARTIAL HEARING LOSS

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I

It is now more than ten years since the publication of the first account relating the use of irradiation as a therapeutic agent in reducing the extent of benign hypertrophy of the lymphoid tissue of the nasopharynx. Since the original report of Crowe,⁵ many other otolaryngologists have employed irradiation in the treatment of a wide variety of conditions associated with hyperplasia of the lymphoid elements of the nasopharynx.

The irradiation of the pharyngeal ostia of the eustachian tubes was undertaken by Crowe in an effort to relieve partial or complete obstruction of the tubes by lymphoid tissue. This therapy was based on the theory that partial or complete tubal obstruction was related to some degree of hearing loss. Two of Crowe's original tenets were that this type of obstruction was a common etiological agent in the production of the partial hearing loss of many children and that continued obstruction might cause permanent hearing disability.⁵

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Considerable controversy has arisen on the part of the medical profession since the use of irradiation therapy became more widespread in the latter half of the present decade. Many otolaryngologists have reported successful results from this type of therapy, whereas others have refused to employ it.

At the New Haven Hospital, irradiation of the nasopharynx with radium has been employed in the treatment of a variety of conditions since 1946. More than 250 patients have been treated thus far. It is the purpose of this paper to analyze the results of this therapy in a selected group of these patients who showed partial hearing loss. In these cases radium was employed in an effort to improve hearing acuity insofar as possible or to prevent further hearing loss.

With this view in mind all of the patients who have received a full course of radium treatments, who were under the age of 16 years at the onset of treatment, and who were deemed good candidates for therapy by clinical and audiometric evaluation, are examined. In every case a follow-up audiogram has been obtained.

II

Many people have experienced obstruction of the eustachian tube during an acute upper respiratory infection and are aware of the loss of hearing which results. The physiological role of the eustachian tube in equalizing the air pressure within the middle ear with that of the atmosphere is well known. In addition to this function the tube serves as a duct which drains the small amount of mucus which is being formed by the membrane of the middle ear and by the tube itself. When the eustachian tube becomes obstructed, air is absorbed by the membrane lining the middle ear, and the pressure within that cavity becomes less than atmospheric pressure.¹⁴ The ossicular chain and the tympanic membrane no longer function properly. Vibratory impulses impinging upon the outer surface of the tympanic membrane are less efficiently conducted to the inner ear. This pathological process results in various degrees of partial hearing loss, varying from serious impairment (60 db for speech) to a slight disability of which the patient may be unaware. An example of a clinical condition in which this sequence of events occurs in a previously healthy patient is aero-otitis or barotrauma. This finding was common amongst the air corps personnel during the last war. Fowler²⁰ reports changes in the membrana tympani and hearing loss associated with this condition. Prolonged obstruction of any body tube which conducts a secretion is known to lead to stasis and infection. This principle, well known to the pathologist,

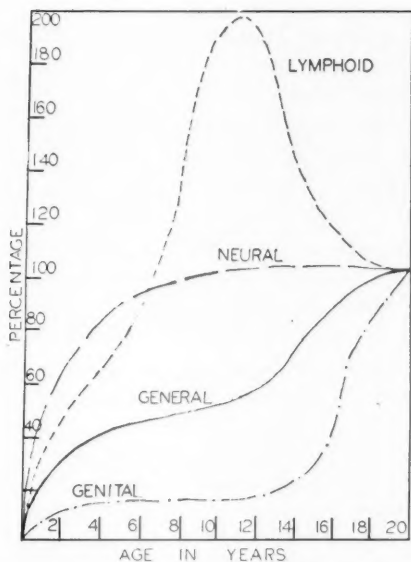


Fig. 1.—The relative growth rates for three body tissues compared to the percentage growth of the body as a whole (Scammon).

is applicable to the middle ear and its draining tube, the eustachian tube. When obstruction of this tube persists for a sufficient length of time, otitis media and permanent changes in the middle ear almost invariably result. These changes consist largely of mucosal thickenings and adhesions.¹⁷ It is rare, however, that the otolaryngologist is able to say that a tube is so completely obstructed that the Valsalva test will not reveal changes in the air pressure of the middle ear with forced expiration. A severely obstructed ureter may lead to pyonephrosis yet still be capable of conducting some urine to the bladder. In a similar manner it is not improbable to assume that states of incomplete obstruction of the eustachian tube exist, and that these states are deleterious to the proper function of the middle ear. Indeed Crowe⁷ feels that this type of obstruction is an underlying factor in many cases of hearing loss, and that if the condition is not relieved, permanent damage resulting in partial hearing loss will result.

Arguing that this condition of partial obstruction is an important factor in the production of partial hearing loss in children, the otolaryngologist would be prompted to ascertain the causes of

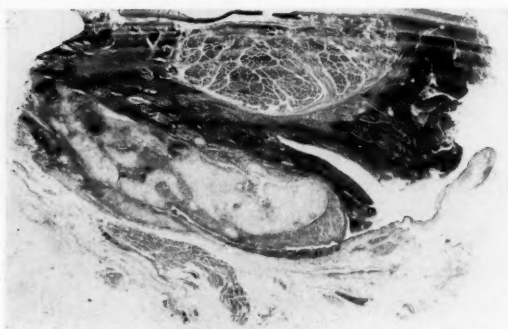


Fig. 2.—Photomicrograph of pharyngeal end of eustachian tube showing lymphoid tissue up the lumen impossible to remove surgically.

such obstruction and remove them if possible. Fig. 1 is taken from the White House Report for 1932 (Scammon). It shows the relative growth rates of three body tissues compared to the percentage growth of the body as a whole. Notice that from the first few months of life and until 6 years of age the neural tissue and the lymphoid tissue are the two most rapidly developing masses. From the age of 6 years until maturity is accomplished, the lymphoid tissue becomes the most rapidly growing tissue by far. This immense predominance of lymphoid growth is most marked between the ages of 7 and 15 years. It is perhaps the generalized activity of lymphoid tissue in this period which causes the hypertrophy of these elements in the nasopharynx and about the eustachian tube. This hypertrophied lymphoid tissue is often observed near the pharyngeal ostium of the eustachian tube during a nasopharyngoscopic examination. Indeed this lymphoid tissue is believed to be the most common cause of chronic partial obstruction of the eustachian tube in children. In aero-otitis and other conditions the same lymphoid obstruction is observed in adults. (Rare causes of eustachian blockage are inspissated mucus plugs and malignant growths. These conditions will not be discussed.)

Therefore lymphoid tissue seems to be the chief offender underlying chronic eustachian obstruction and partial hearing loss. The relative predominance of this tissue in the child's compared to the adult's nasopharynx may explain the greater frequency of eustachian tubal obstruction in children, that is, the chronic obstruction caused by lymphoid tissue. This is borne out by the lymphoid growth curve in Fig. 1. A secondary infection of this hyperplastic

tissue is common, reflected as it often is in chronic tonsillitis. The faucial tonsils, however, are rarely if ever directly responsible for eustachian obstruction because of their distance from the ostium.

Therapy, therefore, is aimed at removing as much of the lymphoid tissue about the tube as possible. The patient is first treated for any infection which may be present. The adenoids are then removed; if the tonsils are chronically infected they should be removed also. Despite the most vigorous chemotherapeutic and surgical treatment the hearing loss may persist. The reason for this persistence becomes more apparent when one observes Fig. 2. This is a photomicrograph of the eustachian tube of an aviator killed during the last war. The photomicrograph is made from a slide of a section through the pharyngeal end of the eustachian tube. Notice the large amount of lymphoid tissue well up the tube and out of the reach of the surgeon. The continued existence of these masses of lymphoid tissue explains the poor results observed in many cases of this type treated by surgical methods alone. When impairment of hearing persists despite adequate chemotherapy and adenoidectomy, the otolaryngologist searches for another method which will enable him to reduce the lymphoid tissue obstructing the tube.

It has long been known that lymphoid tissue is sensitive to irradiation.^{1, 15} Indeed, recent evidence proves that it is the most sensitive tissue in the body, with the possible exception of the germ cells,¹⁰ to the effects of irradiation. A sufficient quantity of this type of energy applied to lymphoid tissue causes marked regression in the size of the nodules and decreased activity of the cells in their germinal centers.¹⁵ The extreme sensitivity of lymphoid tissue to irradiation is the basis for the treatment of hypertrophied pharyngeal lymphoid tissue by this means.

The three most available sources of energy for irradiation treatment are the roentgen-ray machine, radium, and radon gas. All three of these may be employed in the treatment of this condition. A disadvantage of the roentgen-ray machine is that irradiation of the skin overlying the tubal orifice must be effected. Radon gas, whilst obtainable in small containers, has the inconvenience of a short half-life and necessity for frequent standardizations. It is only of practical value within a short distance of a radon supply center. Radium is the most convenient method of accomplishing irradiation of the nasopharynx for most otolaryngologists. Once standardized it remains active within very small variations of intensity for many years. It is employed in an especially designed nasopharyngeal applicator.

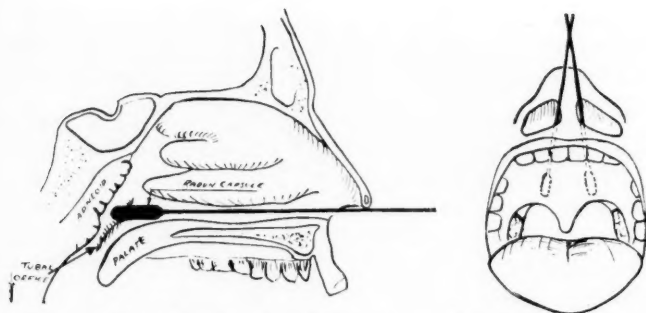


Fig. 3 and 4.—Location of applicators in nasopharynx (Fowler).

The applicator consists of a thin flexible rod, 8 in. in length, which supports a small brass or Monel metal capsule at its end. In this capsule is placed a quantity of radium salts. The standard amount used is 50 mg. The patient's nasopharynx may be prepared with an anesthetic spray, but this is often unnecessary. The applicator is then inserted along the floor of the nasal cavity. It passes beneath the inferior turbinated bone and comes to rest just medial to the pharyngeal ostium of the eustachian tube. Treatment is administered bilaterally, an applicator being inserted through each nostril. The handles of the applicators may be bound together, thus forcing the inserted tip containing the radium salts closer to the tubal orifice. Fig. 3 shows the relationship of the applicator once inserted to the pharyngeal orifice of the eustachian tube. Fig. 4 shows the relationship of the tips of the applicators to the orifice of the tube which lies some 0.5 to 1 cm lateral to the plane of the midsection. In Fig. 4 the handles are shown bound together, and the tips of the applicators are forced laterally towards the ostia.

The applicators are kept in place for a 12-minute period; three such doses administered at 14-day intervals constitute a course of therapy. This is a total dosage of $3 \times 50 \times 12$ or 1800 mg-min. to each side. Earlier Crowe had advocated a treatment lasting only $8\frac{1}{2}$ minutes; this would comprise a total dosage of $3 \times 50 \times 8\frac{1}{2}$ or 1275 mg-min. to each side. Later he felt that the 12-minute treatment would be more advisable.¹² At the present time the 12-minute or 1800 mg-min. total dosage is used. At the New Haven Hospital both the 1275 mg-min. and 1800 mg-min. dosage have been employed, the latter being used at the present time.

As early as six weeks after a course of radium treatments one may be able to detect changes in the nasopharyngeal lymphoid tis-

sue marked by atrophy.^{1, 15} Usually such changes are evident by the end of the second month after the last treatment. There is quite often a subjective improvement in the patient's symptoms. How long these changes persist is unknown. In the case analysis which follows are presented the results of such irradiation therapy in a group of 50 patients.

III

Here are presented the results of an analysis of 50 cases of partial hearing loss treated by radium at the New Haven Hospital during the years 1946-1948. They represent all the patients receiving such therapy who met the following conditions:

- I Patients were 15 years of age or younger at the time of the first treatment.
- II Patients received a pretherapy examination including an audiogram.
- III Patients were deemed candidates for therapy as a result of the examination.
- IV Patients received a complete course of treatments—minimal dosage of 1275 mg-min. (each side).
- V Patients had a post-therapy audiogram and examination at an interval of 3 months or more.

Each record was analyzed for the following data:

CASE RECORD ABSTRACT FORM

1. Age
2. Sex
3. Duration of hearing loss in months
4. Involved side or sides
5. History of otitis media
6. History of otorrhea
7. Condition of tonsils
8. Condition of adenoids
9. Condition of eustachian tube
10. Prevalence of lymphoid tissue in the nasopharynx
11. Condition of membrana tympani
12. Average decibel loss in frequencies 512, 1024, 2048 before treatment

13. Average loss in same frequencies after treatment
14. Change in audiograms
15. Interval between examinations
16. Dosage of radium employed
17. Evaluation of results of therapy on the part of the patient
18. Evaluation of results of therapy by the examiner

Sex and Age. Of the 50 patients, 26 were males and 24 were females. Table 1 shows the age distribution. The average age was 11.4 years (see Fig. 1).

TABLE 1

AGE (YEARS)	NUMBER	PERCENTAGE
5	1	2
6	0	0
7	2	4
8	4	8
9	5	10
10	4	8
11	4	8
12	11	22
13	9	18
14	4	8
15	6	12
	50	100%

Duration of Hearing Loss. The duration of the hearing loss was recorded in months until 60 months; those cases of greater than 60 months' duration were recorded as over 60 months. The average duration was 22.1 months. Table 2 shows the distribution.

TABLE 2

DURATION (MONTHS)	NUMBER	PERCENTAGE
0-10	7	14
11-20	6	12
21-30	8	16
31-40	5	10
41-50	1	2
51-60	3	6
over 60	20	40
	50	100%

Involved Side. In 45 patients there was bilateral hearing loss, while in 5 patients there was only unilateral disease. Thus 90% of the patients had bilateral impairment of hearing.

History of Otitis Media. Thirty-one patients or 62% had evidence of otitis media in the past or present; of these, 27 or 54% had bilateral otitis and 4 or 8% had unilateral otitis. Nineteen or 38% had no history of otitis media.

History of Otorrhea. Twenty-eight patients or 56% had a history of otorrhea. Twenty or 40% had bilateral otorrhea, whereas 8 or 16% had unilateral drainage. Twenty-two or 44% had no history of otorrhea. Table 3 is a summary of the above findings.

TABLE 3

	HEARING LOSS		OTITIS MEDIA		OTORRHEA	
	No.	%	No.	%	No.	%
No history	0	0	19	38	22	44
Unilateral history	5	10	4	8	8	16
Bilateral history	45	90	27	54	20	40
	50	100%	50	100%	50	100%

Tonsils and Adenoids. Thirty-nine patients or 78% had a history of tonsillectomy. In 11 patients or 22% the tonsils were present at the time of therapy; in all of these the tonsils looked "benign." Forty-seven patients or 94% had a history of adenoidectomy; several had repeat operations before therapy. Three patients had no history of adenoidectomy noted; in these 6% the adenoid tissue was not enlarged.

Eustachian Tube. In all of the patients partial obstruction of the eustachian tube was suspected. In only 10 patients or 20% was this obstruction demonstrated by masses of tissue obstructing the eustachian orifice. In 5 patients or 10% bilateral obstruction was noted; in the remaining 10% the obstruction was unilateral. In 10 patients or 20% the tube was obstructed to the Valsalva test.

Lymphoid Tissue. In all patients a relative increase of lymphoid tissue was noted. In 16 patients or 32% this was felt to be within normal limits. In 22 patients or 44% hyperplasia was described, whereas in 12 patients or 24% marked lymphoid hyperplasia was present.

Membrana Tympani. In 19 patients or 38% no disease of the tympanic membranes was noted. Twenty-six or 52% had bilateral changes such as perforation, retraction, or scarring; 5 patients or 10% had unilateral disease of the membrane.

Dosage. The average dosage of radium was 1732 mg-min. to each side. More important is the distribution of dosage which is shown in Table 4.

TABLE 4

MG-MIN.	NO.	PERCENTAGE
1275	11	22
1625-1800	35	70
2125-2975	4	8

Audiometric Time Interval. The interval between the initial audiometric determination and the follow-up audiogram was recorded in months. The average follow-up was 9.32 months. Table 5 shows the distribution of the follow-up periods.

TABLE 5

PERIOD IN MONTHS	NO.	PERCENTAGE
3	12	24
4	3	6
5	4	8
6	5	10
7-10	7	14
11-12	10	20
13-24	7	14
over 24	2	4
	50	100%

Audiometric Findings. The audiometric findings are recorded as the average decibel loss in the three frequencies 512, 1024, and 2048. These are three representative frequencies in the range corresponding to that necessary for the comprehension of ordinary speech. It has long been taught that early loss in middle ear disease occurred mostly in the lower frequencies. Crowe⁶ believes that some cases of middle ear disease are manifested by early high tone loss. Other workers do not accept this view. The rule remains for the large majority of cases that most hearing loss which is manifest-

ed by difficulties in understanding speech will be represented by the frequencies chosen. A significant change in audiometric findings is taken as 10 db or more.

Of the 50 patients examined at follow-up, 13 or 26% showed bilateral significant improvement in the audiometric average. Fifteen patients or 30% showed unilateral improvement. Twenty-two patients or 44% showed only slight improvement or no change in their audiometric picture. These findings will be discussed in correlation with other factors.

Evaluation of Results by the Patient and Examiner. At the follow-up examination the patient was asked if he noticed any change in his symptoms. His response was recorded according to the scheme given below. In addition the examiner made an independent conclusion in regard to the efficacy of therapy. This was recorded according to the scale which is shown below. Table 6 shows the results.

TABLE 6

	PATIENT		EXAMINER	
	NO.	%	NO.	%
A	10	20	10	20
B	18	36	31	62
C	22	44	9	18
	50	100%	50	100%

A—marked improvement in condition.

B—noticeable improvement.

C—no change in condition.

D—worsening of condition (none noted).

Thus one has three methods to evaluate the results of the therapy; first, the audiometric examination as reflected in a change in the average decibel loss for frequencies 512, 1024, and 2048; second, the evaluation of the results by the patient; and third, the similar evaluation by the examiner. If we call groups A and B of Table 6 evidence of an improvement in status in the opinion of the patient and examiner respectively, we can show in Table 7 a summary of the three evaluations of results. Using the results shown in Table 7 as indicative of the response of the group, we can proceed to correlate individual factors in the history with the results. We can examine the effect upon the results of such a factor as the duration

of the hearing loss. Table 7 is a summary of the effect of this irradiation therapy on the entire group of 50 patients.

TABLE 7

	IMPROVED		UNCHANGED	
	NO.	%	NO.	%
Audiogram	28	56	22	44
Patient	28	56	22	44
Examiner	41	82	9	18

The correlations described above are presented in the following pages.

Sex and Age. There was no significant change in the percentage of improvement which could be correlated with the age or sex of the patients. One must remember that all the patients were under 16 years of age.

Duration of Partial Hearing Loss. In Table 2 we saw the distribution of the duration of hearing loss in months. In Table 8 these patients are divided into three larger groups: duration 0-20, 21-60, and over 60 months, respectively. The percentage improvement is shown by the three methods of evaluation. Table 7 is shown at the bottom for comparison.

TABLE 8

DURATION IN MONTHS	NUMBER OF PATIENTS	AUDIOMETRIC IMPROVEMENT		IMPROVED BY			
				PATIENT'S EVALUATION		EXAMINER'S EVALUATION	
		No.	%	No.	%	No.	%
0-20	14	10	71	11	79	14	100
21-60	16	9	56	7	45	13	79
over 60	20	9	45	10	50	14	70
TABLE 7	50	28	56	28	56	41	82

From Table 8 one can see that those patients whose difficulty in hearing was of 0-20 months' duration had a better percentage of improvement in all three columns than the group as a whole. Those of 21-60 months' duration almost paralleled the group, whilst those of over 60 months' duration were somewhat lower in percentage improvement than the whole group. From this table, one may con-

clude that the longer the duration of the hearing loss, the poorer the prognosis for improvement becomes. This difference is not so great that one would be inclined to deny radium therapy to the patients whose hearing losses were of long duration.

Involved Side. Of the 5 patients who showed unilateral involvement, 2 showed improvement. The group is too small for any conclusions to be drawn.

Otitis Media. Of the 19 patients or 38% who had no history of otitis media, audiometric improvement was noted in 12 or 63% of that group. Improvement as indicated by the patients was recorded in 11 or 57%; improvement by the examiner was seen in 14 or 73%. These percentages are only slightly different than the group as a whole. One may conclude that the presence or absence of otitis media does not affect the prognosis for improvement.

Otorrhea. Of the 22 patients with no history of discharge (see Table 3), audiometric improvement was recorded in 14 or 64% of that group. Thirteen or 56% of the patients noticed improvement whereas the examiner thought 19 patients improved, or 86% of this group. The results are slightly better than the group taken as a whole. One concludes that the presence or absence of otorrhea does not markedly affect the chances for significant improvement after therapy.

Tonsils and Adenoids. No significant change in percentage improvement could be shown in comparing the 39 patients or 78% who had a history of tonsillectomy to the rest of the group. Since only 6% had no history of adenoidectomy, no correlation was attempted.

Eustachian Tube. Of the 10 patients who had obstructed eustachian tubes, either bilaterally or unilaterally, 5 or 50% showed audiometric improvement. Five or 50% of the patients felt improved and 8 or 80% were thought improved by the examiner. In most cases the tubes were patent at the follow-up examinations. The group is small; the improvement is somewhat less than that of the whole group. No conclusions are drawn regarding the degree of obstruction.

Lymphoid Tissue. Comparing the results in those cases with marked hypertrophy of lymphoid tissue to those with moderate or minimal hyperplasia, no changes were noted. Here again the degree of hyperplasia or obstruction does not seem to affect the results.

Membrana Tympani. In the 19 patients or 38% who had no disease of the tympanic membranes, improvement was noted by

audiogram in 10 or 52%. Ten or 52% noted improvement whilst the examiners detected improvement in 16 or 84%. These figures do not vary markedly from those of Table 7.

Follow-up Time Interval. In Table 5 one sees the distribution of the follow-up intervals of the patients. Grouping the patients whose follow-up interval was 6 months or less as compared to those whose interval was 7 months or more, one can demonstrate no significant differences. Of the 3- to 6- month group audiometric improvement was seen in 13 or 54% of this group. Patients noticed improvement in 14 or 58% of the cases; examiners thought the patient improved in 20 instances or 83%. These figures closely resemble those for the whole group given in Table 7. Thus one concludes that the 3-month minimum for follow-up examination was sufficiently long.

Dosage of Radium. Comparing the groups in Table 4 with the results of therapy, one can determine the percentage improvement in each group. Comparing those patients who received the minimum dosage of 1275 mg-min. to the rest of the patients, one finds the results shown in Table 9 below.

TABLE 9.

DOSAGE		AUDIOGRAM		IMPROVED BY PATIENT		EXAMINER	
MG-MIN.	NO.	NO.	%	NO.	%	NO.	%
1275	11	5	45	5	45	9	82
1600 or more	39	23	59	23	59	32	82

Thus it appears that the results in that group of patients who were treated with three 8½-minute applications are not so good as the group as a whole (Table 7), and significantly worse than the remainder of the group who received over 1600 mg-min. of irradiation.¹⁶

IV

We see in this paper a group of patients who have received radium therapy for symptoms of partial hearing loss associated with some degree of nasopharyngeal lymphoid hyperplasia. The age of the patients selected ranges from 5-15 years; it is perhaps not coincidental that their average age is 11.4 years, or close to the peak of the curve (Fig. 1) which represents the activity of lymphoid tissue growth in the body.

One would assume that partial obstruction of the eustachian tube by lymphoid hyperplasia would occur most frequently in that age group (3-7 years) which shows the greatest number of large and perhaps infected tonsils. It must be remembered that the faucial tonsils are well defined masses of tissue whereas the adenoids and other lymphoid elements in the nasopharynx are more scattered. Perhaps the lymphoid tissue about the eustachian ostium follows the growth curve for the lymphoid tissue of the body as a whole. If this is the case, radium therapy might best be given between the ages of 6 and 17 years when the relative lymphoid growth is at its greatest height. Therapy in the adult has been reported useful when hyperplasia is suspected as in *aero-otitis*.²⁰ In general, results in adults are much less satisfactory than in children. This is probably the result of two factors; first, the lymphoid tissue is less likely to be the cause of the obstruction, and second, the obstruction is usually of much longer duration.

Factors which influenced the results in this analysis are many. It is shown that the longer the partial hearing loss exists, the less the chance for significant improvement. Table 8 demonstrates this point. While the differences are significant, they do not preclude treatment in a case otherwise calling for radium therapy.

The results with the greater dosage of radium are better than those from patients receiving a shorter dose (Table 9). In fact, of the four patients who received over 2100 mg-min. of radium, improvement was seen in three. Crowe's opinion in regard¹² to the preference of the 1800-mg-min. to the 1275-mg-min. dosage is affirmed. It is conceivable that the dosage employed at present may still be too small.

Other factors analyzed did not seem to alter the prognosis for improvement. The age and sex of the patients within this group, the absence or presence of middle ear disease as manifested by otitis, otorrhea, or diseased tympanic membranes did not alter the rate of improvement. The amount of lymphoid tissue visualized, the patency or obstruction of the eustachian tube as measured by the Valsalva test, the presence of bilateral or unilateral disease, did not significantly change the percentage of improved cases.

The time-interval used for follow-up examination is deemed sufficient within the distribution shown in Table 5. To see whether or not the effect of therapy is permanent, one must have much longer follow-up examinations.

The rate of improvement by each of the three methods of evaluation is shown in Table 7. It is remarkable that the improvement

by audiometric examination is much less than that noted by the examiner's evaluation. In many instances a decrease in the nasopharyngeal lymphoid tissue, the re-establishment of patency of the tube, the cessation of otorrhea, or other factors led the examiner to think that the patient had benefited by treatment although no audiometric evidence was present. These effects, while desirable, are not considered within the realm of this discussion.

The over-all improvement rate of 56% by audiometric determination is good. It is impossible to say what percentage of the patients would have shown improvement had therapy been withheld. The long duration of symptoms in many cases and the previous experience of the otolaryngologist would incline one to believe that the patients who would show spontaneous audiometric improvement would be far fewer than those who showed such improvement after radium. It is important to remember that 22% of the patients received a 1275-mg-min. dosage of radium. Had they received the 1800-mg-min. dosage to each side, the percentage of improved cases might have been somewhat higher.

In evaluation of the patients to be selected for radium therapy one must bear many factors in mind. The patient should be considered in terms of what proportion of his hearing loss can be explained by obstruction of the eustachian tube. If the element of obstruction is suggested to the examiner, and lymphoid tissue is believed to be the cause, radium therapy is indicated. If the patients are young and the disease is relatively brief in duration, one may expect a large percentage of improved cases following therapy. The condition of the pharynx in regard to the degree of hyperplasia, and the status of the middle ear in terms of evidences of disease do not cause one to make a decision concerning therapy. It is desirable that adenoidectomy precede radium therapy.¹⁴ Tonsillectomy should also be performed if the tonsils are large and show evidence of chronic inflammation.

The length of time which one can expect improvement to last is at present unknown. A recurrence of hearing loss associated with the indications for radium therapy previously mentioned would make one consider repeating the radium treatments. A minimal waiting period of one year should precede such repetition.¹⁴

It is largely for the future to tell whether the use of radium therapy will affect the incidence of hearing loss in adults. Should radium be proved to lower the incidence of adult hearing loss, the desirability of its use would be greatly augmented.

In conclusion one must note that the contra-indications of radium therapy are few in number. The wide experience of several men^{2-5, 7-12, 13-16, 18-27} failed to disclose a single instance of radium burn or other mishap. At the New Haven Hospital there has been no undesirable effect recorded. There has been no report of agranulocytosis or aplastic anemia in any patient so treated. The dosage of irradiation employed is so small that the absence of complications is to be expected.¹⁴

V

SUMMARY

1. The paper deals with partial hearing loss associated with hyperplasia of the nasopharyngeal lymphoid tissue.
2. The etiology of the condition in terms of eustachian tubal obstruction is considered.
3. The theoretical concept underlying the use of radium is discussed.
4. The dosage of radium employed and the technique of administering treatment are described.
5. Fifty cases of partial hearing loss in children who have been treated with radium are analyzed. Improvement was found by audiometric examination in 56% of these children. Fifty-six percent of the patients felt improved. Eighty-two of the patients were considered by the examiner to have benefited from therapy.
6. Factors which affect the prognosis for improvement are discussed.
 - a. The longer the duration of the partial hearing loss, the poorer is the chance for improvement.
 - b. The percentage improvement was greater in those patients who had received a relatively larger dose of irradiation.
7. The indications for therapy are mentioned.
8. There have been no complications of radium therapy reported, probably because the dosage was small.

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LXXXIV

FUNCTIONS OF THE PAROTID GLAND

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AND

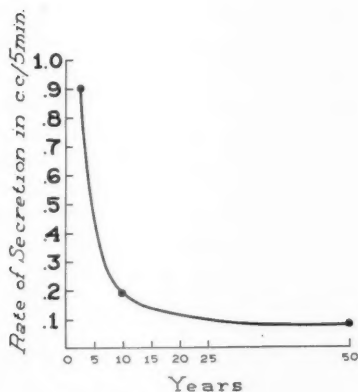
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The parotid gland is a compound tubular or albuminous gland. Its structure consists of clusters of secretory cells around collecting ductules with a relatively meager interacinar stroma of connective tissue. Occasionally small groups of lymphoid appearing tissue are present in the stroma. The secretory cells contain fine basal granules and the cellular secretion contains albumin.

The function of the parotid³⁶ is to secrete a fluid which furnishes protection, moistening and cleansing to the intra-oral structures and upper esophagus, and enzymes that aid in the digestion of certain carbohydrates and nucleoproteins. The parotid saliva is a clear, thin liquid with a specific gravity only slightly greater than that of water. It is normally composed of fluid, salts and ferments, without any mucin and containing very little protein. In the secretion of the quiescent, resting gland the pH varies from 6.0 to 7.9, and the various inorganic salts vary from 30-80% of their respective circulating blood values. Microscopic examination of the normal secretion reveals a few desquamated pavement epithelial cells and a few single goblet shaped cells. The origin of these goblet cells is not definitely known, but is believed to be from the lower end of Stenson's duct where a few mucus secreting cells are normally found. The fluid is sterile and it is impossible to infect the normal parotid gland artificially by retrograde injection of organisms up Stenson's duct.³⁵ A suppurative parotitis can be produced, however, if the organisms are injected into the nutrient artery to the gland or if the duct is blocked after injecting organisms in a retrograde fashion.⁷ This inherent ability of the gland to maintain sterile conditions is believed to be due to the continual secretion of saliva which washes out any organisms that have gained entrance to the duct from the oral cavity, and also to the corkscrew configuration of

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GRAPH 1

Stenson's duct which hinders the retrograde flow of fluid or organisms.

The amount of secretion of the normal resting gland has been measured by many investigators. Lashey in 1906 devised a collecting receptacle in the form of a suction cup that fits accurately over the ostium of Stenson's duct. It is a nonirritating device that allows accurate collection of specimens. In young, healthy people the average secretion of the normal resting parotid gland is $.07 \text{ cc} \pm 2x$ per 5 minutes.^{36, 44} Graph 1 shows the rate of secretion in relation to age. There is a great flow of saliva in infancy, a stable period in healthy middle life, and a marked decrease in old age.^{36, 37} The great flow in infancy is believed to be due to immaturity of the cerebral cortex and to the normal greater vagotonia of infants.

The nerve supply to the parotid gland is derived from both the sympathetic and parasympathetic systems.³⁶ The parasympathetic fibers course with the glossopharyngeal nerve through the chorda tympani to the otic ganglion, and from there through the auriculotemporal nerve to the gland where the end organs are immediately adjacent to the secretory cells. Electrostimulation of the chorda tympani or the auriculotemporal nerve, or administration of pilocarpine (a parasympathomimetic drug) results in a marked increase in the secretory rate and volume and a moderate vasodilatation in the gland. The sympathetic fibers arise from the upper cervical chain and pass through the superior ganglion. Stimulation of this ganglion has practically no effect on the parotid gland but causes an increase in the secretion of the other salivary glands. Sympathetic

stimulation does cause vasoconstriction in the parotid and also an actual contraction of the gland from contractile mesothelial cells in the lining membrane of the ductules.

The stimulation that causes the parotid gland to secrete is carried through nerve tract reflex arcs. A hormonal stimulus has never been found. The main reflex arc is from the tongue to the cerebral salivatory center and back to the parotid. Because of the availability of the parotid and the ease of accurate collection of its secretions, the salivation reflex has been used by investigators for many decades in working out various basic physiologic and neurophysiologic functions. Allen¹ determined that the parotid responds to activating stimuli in a manner similar to the mathematical response of the organs of special sense and contractile muscles. He found the gland to show typical effector response of inhibition and enhancement on strong and weak stimuli of varying strengths of acetic acid on the tongue. It was impossible to establish a fatigued condition on prolonged stimulation. On varying the intensity of the stimulation he found the quantity of the secretion to alter proportionately, but only up to a certain high point. As the stimuli and the quantity of the secretion increased, the specific gravity of the secretion varied only slightly, proving that those secretory fibers of the parasympathetic system which control fluids and salts in the secretion respond more readily to stimuli than do the trophic (or sympathetic) fibers that control the solids in the fluid.

It has been determined by several different investigators that the parotid gland has a normal resting secretion. Anrep and Cannan² measured the blood sugar in the artery and vein of a gland at rest and found that stimulating the chorda tympani nerve increased the sugar consumption by the gland in proportion to the increase in the salivary output. The administration of pilocarpine also increased the sugar consumption by the gland and the salivary output, while atropine gave no effect. This indicated that the gland has an inherent secretory rate which is not under control of stimulation. This was further proved by dividing all the nerves to the gland and demonstrating that the type and amount of secretion of the normal resting gland were maintained.

Normal parotid secretion contains uniform amounts of all of the diffusible components in the circulating blood. In addition it has three secretory products that are different from the blood salts and are perhaps unique for the parotid gland. These are amylase, uric acid and potassium thiocyanate.

Salivary amylase (ptylin) is derived practically entirely from the parotid secretion. It is believed that the salivary amylase usually

plays little part in the digestion of carbohydrates, since it is inactivated by the acid gastric secretion. However, when the salivary amylase has a chance to work it can break down cooked starch 80% completely to dextrins and maltose.^{27, 38} There is usually no glucose in normal parotid saliva, but when it has been found, the ferment maltase has been present also.^{27, 29} Alkaline phosphatase has consistently been found in parotid saliva, and it has recently been determined that it is secreted by the glandular tissue and the ductule epithelium.¹⁷

Uric acid is the most stable chemical in the parotid secretion. It has long been known that saliva differs greatly in amount, type and chemical constituents under individual variations of time and stimuli.^{5, 6} The uric acid content of the saliva has an apparent single regulator. In normal parotid secretion there is 0.6-2.9 mg% of uric acid for males and 0.7-2.3 mg% for females. The amount of dietary intake of purine foods and the extent of urinary excretion of uric acid have no effect on the salivary uric acid. There is also very little change in the content following the mechanical stimulation of chewing paraffin, which increases the salivatory flow. This is in sharp contrast to the other chemical components of the saliva. Morris and Jersey³⁸ noted these great chemical variations in the saliva and found that the uric acid content appeared to fluctuate directly as the stimulation to the end organ itself. That is, the uric acid responds directly to pilocarpine and indirectly to atropine. From these factors it is believed that the uric acid content of the parotid secretion can be used as an index of the actual metabolism of the gland or its cellular activity.

The relationship of the salivary glands, serum thiocyanate and blood pressure has been studied for almost 50 years. Early investigative work suggested that the circulating thiocyanate level in the blood serum was inversely proportionate to the blood pressure. It was believed also that the thiocyanate was formed in the salivary glands from catabolism of sulfur containing amino acids.³⁹ It is supposedly secreted in the saliva and reabsorbed from the intestinal tract. Another possible source of salivary thiocyanate is from detoxication of the small amounts of cyanide which occur in food. The normal serum level is 0.19-1.39 mg% and the normal saliva level is 0.01 mg%. Thiocyanate has been used extensively, and often unsafely, in the treatment of hypertension. There is also a little understood interrelationship of the parotid gland, the thyroid gland and thiocyanate. The administration of thiocyanate lowers the basal metabolism of the body and frequently causes enlargement, often goiterous, of the thyroid. Administration of iodine, which is spe-

cifically secreted by the parotid, will cause complete disappearance of thiocyanate from the saliva.³⁹ Tobacco is supposed to increase the amount of thiocyanate in the saliva. Thiocyanate is absent from the saliva in many types of avitaminosis (pellagra) and in cases of hypertrophy of the parotids. This factor has led to much speculation about the role of thiocyanate in these diseases. At the present time there is some doubt that there is normally any thiocyanate in the blood or saliva, since newer methods of testing have shown errors in the older methods of measuring it.

The factors that influence the parotid secretion may be classified as (1) local, (2) general, (3) nervous system, (4) gastrointestinal.

Local. Local mechanical irritation to the buccal mucosa has no effect on the secretion, nor does muscular activity of the jaws, tongue and pharynx. Local irritation on the tongue results in increased secretion.

General. There is no relationship of an individual's height, weight, pulse rate or blood pressure to the parotid's secretion. The secretion pressure is always much higher than the blood pressure. Dehydration has a marked effect on the amount and type of secretion, as also does infection or inflammation of the gland itself. Old age seems to reduce the amount of secretion and also the amylase content. The marked increased flow of saliva in infancy is probably a cerebral function.

Nervous System. Sleep, hypnosis and fear greatly decrease the salivary flow. The emotions in general affect the secretory rate to a moderate degree. The secretory response of the gland to conditioned reflexes has been proved to be transitory. Abnormalities of the higher cerebral centers have a marked effect on the salivary flow. Strongin and Hinsie⁴⁴ have shown that people with manic-depressive psychosis have only about one-half the normal amount of resting parotid secretion, while severe schizophrenic patients have many times the normal amount. From these facts they can unequivocally differentiate the true psychotics from the psychoneurotics, who have a normal rate of secretion.

Gastro-intestinal. Hunger and fasting cause a decrease in parotid secretion, while satiation of the hunger increases the flow. Gastric distention causes an increased flow, while food already in the stomach has no effect on the secretion.³⁸ The marked salivation associated with noxious products in the stomach which causes nausea is known to everyone. There are reported incidents of increased flow of saliva associated with many types of gastro-intestinal abnor-

malities. Many clinicians report an increased salivary flow with pylorospasm and cardiospasm. Pearson⁴⁰ reports a child that had rapid swelling of the parotids and a greatly increased flow of saliva when he had intestinal colic. This syndrome could be re-established by manually manipulating the stomach and intestines through the abdominal wall.

Clinical and experimental evidence accumulated for the past 75 years has shown that there exists some inherent type of relationship between the salivary glands (primarily the parotids) and the organs of internal secretion. Embryologically the salivary glands are derived from outpocketings of the enteric canal in a fashion similar to the development of many of the intra-abdominal organs. John³⁰ and Birnkrant⁹ have summarized a large series of foreign reports on clinical and experimental observations on the relationships of the salivary glands and associated diseases.

The complications appearing with acute epidemic parotitis which affect the testicles, ovaries, pancreas, breast and central nervous system have long been well known. These complications tend to occur only in people with well developed sexual functions and only rarely in children and the very aged. Stevens⁴³ reported several cases of mumps in which severe midabdominal pain, hyperpyrexia, nausea, vomiting and midepigastic tenderness without rigidity developed in the first week of the disease. Fifty per cent of these cases showed icterus. Garrett²³ reported a patient with acute pancreatitis, glycosuria and orchitis, coming on 10 days after the onset of mumps. Wesselhoeft⁴⁵ found that acute pancreatitis was the second most common complication of mumps. In a large series of hospitalized cases of mumps, Brahdy¹² noted orchitis in 10% and acute pancreatitis in 5%. All of these patients were adults or adolescents, and none of them acquired diabetes. In two cases of acute pancreatitis following mumps, autopsy showed typical pathology, and in one of them microscopic examination showed hyaline degeneration of the islands of Langerhans.²⁴ Kremer³⁴ reported two cases of true diabetes mellitus arising during convalescence from mumps. Neither patient had had any obvious abdominal pain. The diabetes remained stationary for over four years. The blood amylase is found to remain elevated for several weeks in cases of uncomplicated mumps.¹⁸ An elevated serum lipase in conjunction with even very mild abdominal pain is definite proof of an acute pancreatitis.¹³ A plausible hypothesis to explain this definite organ relationship in complications of mumps is that there is an organ specificity to the causative virus (organotropic).

The relationship of parotid function to other organs has been an intriguing study. There is an apparent abnormal preponderance of enlargement and hyperfunction of the parotids in men and women at their climateric and menopause. Mahr⁹ found parotid hypertrophy associated with atrophy of the sexual organs, and Freudenberg²¹ reported a similar case with celiac disease and diabetes. As a corollary finding, Phillips⁴¹ reported a woman with nontender enlargement of the parotids which occurred during two successive pregnancies and subsided between times. Her saliva was microscopically clear and sterile. Harkin²⁶ reported two similar associations between parotid hypertrophy and pregnancy. One of his patients had painless enlargement of the parotids during six successive pregnancies; the glands returned to normal size between times. She used the rapidly enlarging parotids as the first sign of pregnancy.

Several instances of enlarged parotids and concurrent thyroid disease are reported. Many reports have appeared recently of bilateral painless enlargement of the salivary glands occurring during the thiouracil treatment of hyperthyroidism.¹⁵

The relationship of enlarged, apparently hyperfunctioning parotids and diabetes has been repeatedly reported in medical literature for the past 75 years.^{16, 20, 23, 30, 32} Flaum²⁰ decided to reverse the procedure and investigate the function of the pancreas in cases of asymptomatic chronic symmetrical parotid enlargement. Of 27 such patients, 16 showed frank glycosuria and high fasting blood sugar values while on sugar-free diets. These patients had not known of their diabetes before and came to the clinic for other unrelated complaints. The remaining 11 patients all showed a latent diabetic curve on glucose tolerance tests, but did not have glycosuria. John³⁰ and Dobreff¹⁶ report cases in which chronically enlarged parotids regressed after moderately severe diabetes was brought under control with insulin. Kenawy³² studied a group of people from the upper Nile Valley, where chronic enlargement of the parotids is endemic, and found that 10% had diabetes; half of these cases were of the latent type proved only by the glucose tolerance curve. Flaum²⁰ found that the mildly diabetic, middle aged, obese, hypertensive patients all showed variable degrees of asymptomatic hypertrophy of both parotids, and he believed they should be considered a type. The most famous case was studied intensely and reported at great length in the Italian literature.³⁰ This patient had diabetes and had an alternating overflow of sugar in his saliva and urine. When the glycosialorrhoea was apparent there was a salivation of several liters a day and the urine was free of sugar; then the saliva would decrease

and become sugar-free and he would spill sugar in the urine. Freudenberg²¹ reported several cases of enlarged parotids associated with diabetes in which he had complete clinical and laboratory studies and long follow-ups. Two of his patients were identical twins whose parotids enlarged after the onset of diabetes at 5 years of age. They both later developed celiac disease with very low pancreatic enzymes.

Whether the parotids ever hypertrophy or undergo hyperplasia to increase their function has never been proved. This aspect of parotid enlargement has been the subject of many hypotheses which have been based on clinical observations, application of known physiological and biochemical facts, and occasionally on animal experiments. The general increase in medical knowledge has subsequently proved most of the hypotheses wrong. The question seems to be whether the parotids can increase their function to cover a deficiency of some other organ that has a similar function.

Because of the similarity between the parotid gland and pancreas in embryologic origin and function, their relationship in disease, and the apparent parotid hypertrophy in cases of diabetes, the main search has been to locate a parotid carbohydrate regulating hormone similar to that of the pancreas. Between 1915 and 1930 many experiments were performed, mainly in Germany and Italy, attempting to prove or disprove the presence of a carbohydrate regulating hormone from the parotid. The human parotid responds to ligation of its duct by atrophy of the acini occurring over the following several weeks with replacement of the shrunken gland by fibrous tissue. During this investigative period many pathologists believed that there was an accumulation of islands of cells in these atrophic glands to suggest Langerhans like bodies.³⁵ These concepts became so strong in Germany that great numbers of people with diabetes were having their parotid ducts ligated on the theory that this would force the hypothetical hormone into the circulation. After the results of a large series of cases were found not to warrant this procedure, it was given up. The most recent and best controlled experimental work on this concept was reported by Birnkrant⁹ in 1940. He performed partial and complete parotidectomies in a controlled series of rats. As in the older experiments with complete parotidectomies, the blood sugar fell but the fall was only temporary. He ruled out the effects of surgery as the cause of the post-operative fall in blood sugar and believed he had proved that the drop was due to the removal of a substance antagonistic to insulin that was in the parotid gland. In his operated animals there was no apparent functional or pathological change in any of the other organs. When the parotids were only 90% removed there was not

the typical blood sugar response. In a reverse manner he produced a definite but temporary rise in the blood sugar by irritating the parotid gland.

John,³⁰ in 1933, summarized the foreign literature on the subject of the parotid hormone and also attacked the problem by studying the parotid gland in pancreatectomized diabetic animals. He believes he has shown by his experiments that the parotids produce a substance that normally stimulates the pancreas to function. In a like manner the parotid will have a compensatory hypertrophy and hyperplasia when the pancreatic insulinogenic function begins to fail. In other words, this would cause an endocrine hyperfunction of the parotid. Best, Scott and Banting found an abnormal amount of insulin in the parotid gland, but they thought it was due to extravasation from the blood.³⁰

Clinical disturbances in function of the salivary glands are not rare and are seen most frequently by the laryngologists and dentists.²² The chief complaint of a decreased function is a dry, sticky mouth (xerostomia). The most frequent cause of this is a markedly depressed mental state, and good therapeutic results have been obtained by psychiatric treatment. Occasionally organic lesions can account for xerostomia. Organic dusts, metal dusts and botulism have been proved to disturb the secretory nerve end organ so that the reflex arc in response to taste stimuli is broken up. This nerve block can be by-passed successfully by administering pilocarpine before each meal. Actual central nervous system disease that causes loss of salivation is extremely rare.

An increased salivation (sialorrhea) is quite frequent and is very troublesome in Parkinson's syndrome and following epidemic encephalitis. It is not known whether this is an irritative phenomenon or a release from inhibitors after degeneration of the affected nerve tissue. Enlarged parotids have not been reported in these cases of sialorrhea.

Drugs that cause salivation are mercury, gold, copper, iodine, muscarine, tobacco, bromides, arsenic, potassium chlorate, pilocarpine, bismuth and lead. Drugs that decrease salivation are opiates and belladonna.

Investigation of the form and function of the parotid gland for diagnosis of abnormalities is not well systematized. Accurate diagnosis of chronic infections and neoplasms of the gland was greatly enhanced by the method of lipiodol visualization of the duct system by Sicard and Forestier in 1921. The normal and abnormal appearance of the sialograms have been carefully worked out in the

United States.^{8, 10, 15, 25, 28, 31, 33, 40, 42} Blady and Hocker¹⁰ were able to make a correct diagnosis of parotid carcinoma by its characteristic sialogram in 65% of a large series. Sialography has been used to good advantage in localizing obstructing calculi and differentiating types of chronic infections.

Cultures of the parotid saliva should be done, as well as microscopic examination of the secretion. The volume and rate of secretion of the quiescent resting gland can easily be obtained. The level of the salivary uric acid is an accurate measure of the gland metabolism and function. The amount of salivary amylase should be determined in conjunction with serum amylase. The thiocyanate level of the saliva is supposed to vary in certain diseases, but recent work tends to indicate that the colorimetric measure may be completely misleading. A biopsy for histological examination is the only way to differentiate true Mikulicz' disease from the many systemic, neoplastic or chronic infective agents that can cause a chronic symmetrical asymptomatic enlargement of the parotid glands.

SUMMARY AND CONCLUSIONS

Scattered reports in the medical literature for the past 75 years have been reviewed and consolidated in an attempt to get a clearer picture of the normal functions and forms of the parotid gland.

Many reports of functional abnormalities of the parotid gland have also appeared during this period. The similar embryologic origin of the parotid gland and other internal organs, and similarity of its function to that of the pancreas have stimulated a great deal of literary conjecture, animal experimentation and clinical observation to attempt to find a carbohydrate regulating hormone in the parotid. The opinions of the investigators who performed the best controlled experiments are at variance, but they all agree that there is a hidden, poorly understood factor in the parotid gland that has an effect on the circulating blood sugar. Whether this factor is a substance antagonistic to insulin or whether it has a pancreas stimulating function is debatable.

The presence of asymptomatic enlargement of the parotid glands in association with other diseases is unquestionable. The possibility that the enlargement is a functional hypertrophy to compensate for a deficiency of some other organ has been considered. No reported investigative work has yet solved this interesting problem.

A plan of procedure for the laboratory investigation of affections of the parotid glands is suggested as an aid in the diagnosis of disturbances in their form and function.

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FURTHER EXPERIMENTAL STUDIES OF THE TOXIC
EFFECTS OF STREPTOMYCIN ON THE CENTRAL
VESTIBULAR APPARATUS OF THE CAT

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In a previous article,¹ evidence was presented of damage to the central portion of the vestibular mechanism of cats by streptomycin, administered parenterally. The purpose of this paper is to report upon further statistical evidence of such pathology, based upon a larger series of animals.

As before, three separate methods of investigation were employed: (1) vital staining; (2) routine histopathologic study of stained brain specimens; and (3) the surgical destruction of the vestibular nuclei on one side of the brain stem.

VITAL STAINING

Vital Staining. When certain dyes, such as trypan blue, are injected into the blood stream of an animal, the dye can be detected in all of the tissues and organs of the body except those of the central nervous system. However, if one of these dyes is introduced into the cerebrospinal fluid, the central nervous system then becomes stained. This phenomenon has given rise to the concept of the hemato-encephalic barrier. The exact site of this barrier is disputed. In a previous article¹ some of the theories as to its location were discussed.

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This work was aided by a grant from the National Institute of Health of the United States Public Health Service.

It is well recognized that under certain conditions involving trauma or disease of the central nervous tissues, the blood-brain barrier is broken down, allowing the cells of the affected areas to take up the dye from the blood stream. Thus, when trypan blue is injected intra-arterially, it is a good indicator of central nervous system damage, permitting a rapid survey even with the naked eye.

In our preliminary experiments with cats which had become ataxic from the administration of streptomycin, it was found that in some of the animals certain portions of the brain and spinal cord vitally stained with trypan blue. Therefore, we felt that it would be of value to continue this line of investigation.

Control Studies. Fourteen healthy adult cats were used as controls. Each of these animals, under nembutal anesthesia, received an injection of 20 cc of a sterile isotonic saturated solution of chemically pure trypan blue into the right carotid artery in the direction of the heart. When trypan blue is thus injected into the cat, a high concentration of the dye is carried into the right subclavian artery, thence up through the vertebral artery to the base of the brain. Forty-five minutes to one hour after the injection of the dye, the cats were sacrificed by an injection of 25 cc of 10% formalin into the left carotid artery in the direction of the brain. The brain, spinal cord and temporal bones were immediately removed and prepared for pathological study.

In none of these control animals was there gross or microscopic evidence of trypan blue staining of the brain tissue except around a stab wound of the cortex which had been inflicted in several of the controls to test the effectiveness of the trypan blue technique. For the stab wound method we are indebted to the excellent work of Macklin and Macklin.² In eight of the nine controls (89%) in which the stab wound was made, the nervous tissue about the traumatized area showed gross and microscopic trypan blue staining.

Toxicity Studies. Thirty-six healthy adult cats which had shown good vestibular responses to the turning test were given toxic doses of streptomycin sulfate by the subcutaneous route until the vestibular responses were abolished. The average total amount of streptomycin for each cat was 14.0 gm given over a period of two weeks. The average daily dosage of 1.0 gm per cat was approximately 0.3 gm of streptomycin per kilogram of body weight. Twenty of the animals were given the total daily dose in one injection, while 16 animals received the same total daily amount in three divided doses of 0.33 gm each. At the end of the two-week course of streptomycin, each animal received 20 cc of the trypan

blue solution and was sacrificed 45 minutes to one hour later with 10% formalin, as previously described for the controls.

In the 16 cats which had received streptomycin in three divided daily doses, intracellular trypan blue was found in the brain cells in eight (50%) of the specimens. The areas of the brain which took up the dye are described below. In the 20 cats which had received streptomycin in one daily dose, there was no microscopic evidence of trypan blue staining in any of the brain sections.

ROUTINE HISTOPATHOLOGIC STUDIES

Controls. The brains of 25 cats which had not been given streptomycin were stained with cresyl violet and phosphotungstic acid. Fourteen of these cats had been vitally stained with trypan blue previously; 11 animals had not been injected with the vital stain. Of the 25 specimens only one (4%) yielded any evidence of pathologic changes.

Toxicity Studies. The brains of all 36 cats which had been given streptomycin and vitally stained with trypan blue were subsequently stained with cresyl violet and phosphotungstic acid. An additional 13 cats were given the same total dosage of streptomycin, sacrificed and the brains stained with the same routine histopathologic methods. A few brains were also stained with the Bodian silver impregnation stain.

Of the 49 specimens, 29 (59.2%) showed definite pathological lesions. In 20 of the brains, either there was no pathology or the findings were doubtful.

Twenty-five of these cats had received streptomycin in one daily injection of 1.0 gm, while 24 had been given 0.33 gm three times daily. By the routine methods of staining, there was no significant statistical difference between the two groups as to incidence of pathology (56% and 63%).

The lesions were most frequently found in the Purkinje cells of the vermis, the flocculus and nodulus prevailing. Of the brains showing pathology, 92% showed lesions in these areas. No changes were found in front of the pyramis of the vermis, and few in the hemispheres. The cells of the ventral cochlear nuclei were involved in 31%, the reticular substance in 28%, the spinal cord in 24%, Deiters' nucleus and the dentate nuclei of the cerebellum in 21%, the medial vestibular and the fastigial nuclei in 10%, the acoustic tubercle in 7%, and the trapezoid body in 3½%. Mild changes of questionable significance were seen in the cells of the second, and

occasionally of the third, cerebral cortical layers in several of the specimens.

The changes, as a rule, consisted of pyknosis and shrinkage of the nerve cells. The degree of change varied from animal to animal, but in only a few instances was there evidence of actual cell loss. As previously stated, the most marked changes were in and around the Purkinje cells. The stag-like dendritic arborization of these cells in the molecular layer of the cerebellar cortex was unusually well visualized in circumscribed areas because of the granules deposited upon it. The endings of the climbing fibers around the Purkinje cells were thickened and the Bergmann cells began to develop glia fibers which often took the appearance of so-called "brush glia."

The pathology of cat No. 117 may serve as an example of the central nervous system changes produced by streptomycin. This animal had received 3 daily doses of 0.33 gm of streptomycin over a period of 14 days for a total of 13.3 gm. At this time the eye responses to the turning test were absent and the cat had developed severe ataxia. One week after the last streptomycin injection, 20 cc of trypan blue solution was injected into the right carotid artery. The animal was sacrificed 45 minutes later and the brain was removed immediately and prepared for histopathologic study.

The most marked pathologic changes were present in the Purkinje cells of the flocculus and nodulus. Fewer changes were found in the tonsils of the cerebellum, and still fewer, in its hemispheres. In all of these areas the nuclei, cytoplasm and apical prolongations were studded with trypan blue staining granules (Fig. 1).

A less intense trypan blue staining, though still of the nucleus and cytoplasm, was found in the lateral (Deiters') and medial (triangularis) vestibular nuclei of the medulla oblongata, the ventral cochlear nuclei, and the acoustic tubercle in which the pyramidal cells stood out because of their blue color. The large cells of the reticular substance and a relatively small number of anterior horn cells of the spinal cord showed a dark blue staining of their nuclei but not of their cell bodies (Fig. 2).

The routine methods of staining showed again the most conspicuous changes in the Purkinje cells of the cerebellum. All transitional stages from mere pyknosis of the nuclei, with or without disappearance of the Nissl bodies, to shrinkage and complete loss of cells were present (Fig. 3). The peridendritic glial network was covered with granules and stood out as "brush glia" (Fig. 4).

In Deiters' nucleus and among the large cells of the reticular substance of the medulla oblongata close to the midline, dark-stained

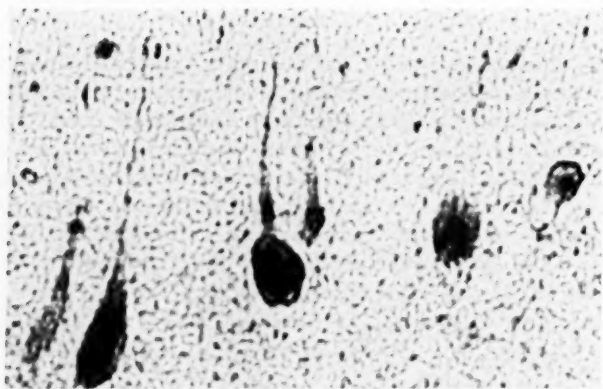


Fig. 1.—Photomicrograph showing Purkinje cells stained with trypan blue-carmin. Four Purkinje cells are deeply stained in cytoplasm and apical dendrites, with a still darker nucleus. The background is slightly pinkish. The dendritic network in some places is studded with blue dots. (x750)

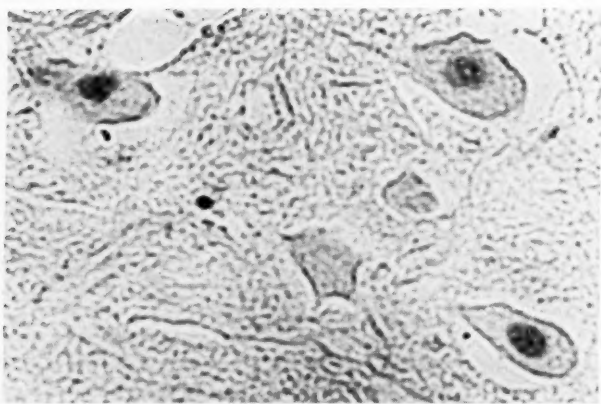


Fig. 2.—Photomicrograph showing anterior horn cells of spinal cord stained with trypan blue-carmin. Three anterior horn cells are seen with the nuclei stained blue, while the cytoplasm and prolongations are unstained. (x680)



Fig. 5.—Photomicrograph showing cells of Deiters' nucleus, pyknotic and shrunken, stained with phosphotungstic acid-hematoxylin. (x340)

shrunken cells were seen side by side with normal ones (Fig. 5). The vestibular fibers running into the cerebellum appeared swollen and darker stained than the rest of the nerve fibers.

SURGICAL DESTRUCTION OF THE VESTIBULAR NUCLEI ON ONE SIDE OF THE BRAIN STEM

Our studies were continued on the effect of unilateral surgical destruction of the vestibular nuclei in cats which had received toxic doses of streptomycin. The rationale of this procedure is based upon the experimental work of Spiegel and Démétriades³ on the vestibular compensatory mechanism. Their experiments and our application of it to cats administered streptomycin has been explained in detail in a previous article.¹ Briefly, in a normal animal the surgical destruction of the vestibular nuclei on the right side of the brain stem produces a nystagmus to the left. However, in an animal in which the central vestibular mechanism has already been destroyed by streptomycin, the surgical destruction of the vestibular nuclei on one side of the brain stem should not evoke a nystagmus. This method, of course, yields information on the central vestibular mechanism only and does not preclude the possibility of concomitant damage to the peripheral vestibular end-organs.

Twelve healthy adult cats were used in this experiment. In the six controls, following surgical destruction of the right vestib-

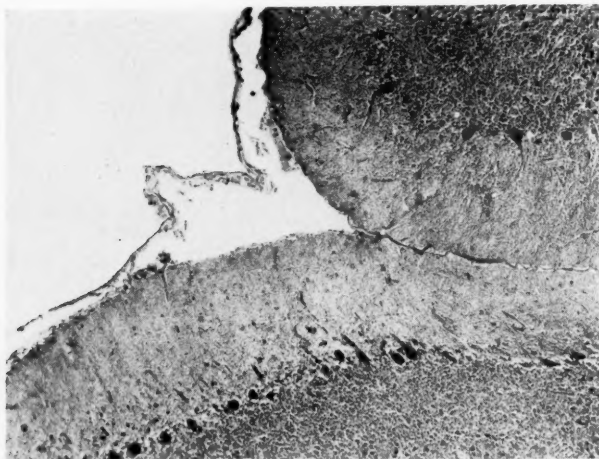


Fig. 3.—Photomicrograph of section of two adjacent convolutions of the cerebellum stained with phosphotungstic acid-hematoxylin. The Purkinje cells on the upper convolution are normally stained, those on the lower are pyknotic, shrunken and partly lost. (x150)

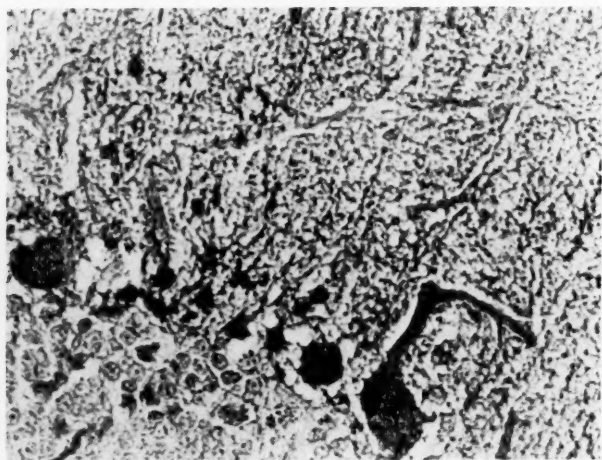


Fig. 4.—Photomicrograph showing two large Purkinje cells, deeply stained with phosphotungstic acid-hematoxylin. Their overlying stag-like dendritic arborization is covered with granules which make the peridendritic network stand out. Between the two Purkinje cells, there are a few dark-stained Bergmann glia cells which have produced glial fibers. (x800)

ular nuclei, there was a constant nystagmus to the left in four animals during the period of 24 hours or longer in which they were observed. In two controls, nystagmus to the left occurred but was not constant. In one of the latter two animals, histologic examination of the brain stem showed the surgical destruction of the vestibular nuclei to be incomplete.

In six cats which had received streptomycin until the eye responses to the turning test had been abolished, surgical destruction of the vestibular nuclei on the right side of the brain stem produced an inconstant nystagmus to the *right* in three of the animals. In the other three cats, there was no nystagmus during the period of observation of 24 hours or longer. Postmortem examination of the brains of these latter three animals showed grossly that the region of the right vestibular nuclei of the medulla had been completely destroyed by the electrocoagulation. Serial sections were made on two of these specimens, and microscopic confirmation of the total destruction of the nuclei was obtained. Thus, at least 50% of the animals in this experiment gave results which support the hypothesis that streptomycin damages the central vestibular mechanism.

SUMMARY

Further evidence is presented on the site of the damage to the vestibular apparatus of the cat by the parenteral administration of streptomycin. Three separate methods of investigation were employed: vital staining, routine histopathologic staining, and unilateral surgical destruction of the vestibular nuclei in the brain stem.

By the vital staining technique, pathologic changes were found in the cerebellum and medulla in 50% of those animals which were given streptomycin in three divided daily doses. In those cats which received streptomycin in one daily injection, no pathologic changes were detected by this method.

Using routine histopathologic stains, evidence of pathology was found in 59.2% of the animals. In these studies, no significant statistical difference in pathology could be found between the group which had received one daily dose of streptomycin and the group which had been given three daily injections of the antibiotic. In only one control animal (4%) were pathological changes found in the brain or spinal cord.

Of the cats receiving streptomycin and showing pathological changes, nearly all had lesions in the vestibular portion of the cerebellum, one-third showed changes in the cochlear system, and one-sixth, in the vestibular nuclei of the brain stem.

The experiment employing the unilateral surgical destruction of the vestibular nuclei in the medulla gave evidence of prior damage to the central vestibular apparatus by streptomycin in 50% of the animals.

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OTOGENOUS EDEMA OF THE BRAIN

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The best known infection of the brain, otitic or rhinogenic in origin, is the acute or the chronic brain abscess. Another infection of the brain and of the same origin is the encephalitis associated with purulent meningitis. From the practical point of view this type of encephalitis is of minor importance because the symptoms caused by it, and the influence it exerts upon the outcome of the individual case, are obscured by the all-important meningitis.¹

Infections of the brain, otitic in origin, which do not proceed to the formation of a brain abscess and are not associated with a purulent meningitis, are problematic as yet. Instances of this type are not frequent and they usually do not terminate fatally. For this reason, this type of otogenous complication is controversial, even to terminology. Apparently terms such as "serous meningitis," "otogenous nonpurulent encephalitis,"²⁻⁵ "otitic hydrocephalus,"^{6,7} "pseudo brain abscess"⁸ and "otogenous brain edema" indicate, in the final analysis, the same morbid entity.

This paper is an attempt to offer an additional clinical contribution to this rather intricate problem.

REPORT OF CASES

CASE 1.—N. B., a white female aged 10 years, had suffered from a common cold four weeks previous to admission, but had not complained of ear troubles. Two weeks later she again had a cold and sore throat. Subsequent to the cold she complained of earache on the left side. Sulfadiazine, 25 gm, and eardrops were administered, but no paracentesis of the drum was performed. There was no discharge from the ear and she felt better until April 17, 1948, three days before admission. Then the earache returned and she was given 10 gm of sulfadiazine. Improvement ensued, but on April 19th, the temperature rose to 103° F. and was associated with a slight chill. Despite the administration of aspirin she had more slight chills followed by profuse perspiration and in the night she complained of pain in the left temporal area, in the left mastoid and on the left side of the neck. On April 20th, at about 10:00 a. m. she had a jacksonian attack on the right side and fell into coma.

On admission on April 20th, the child was conscious and rational and did not seem to be acutely ill. She was excited and resisted examination. The temperature was 101.4° F. and rose during the day to 104° F., associated with chills. There was no jaundice, but slight nausea. The eye grounds were normal. There was a slight tenderness of the atlanto-occipital membrane and a slight hyperalgesia but no other meningeal symptoms. Corneal reflexes were normal. No nystagmus was present but there was paresis of the mouth branch of the right facial nerve. On the right side there was an acute serous catarrh of the tympanic cavity. The left drum was red and bulging and there was a small amount of discharge draining through a small perforation in the anterior and inferior quadrant. There was no sagging of the superior and posterior wall of the external canal and no mastoid symptoms. The spinal fluid was normal and its pressure was not increased. In the blood there were 3,700,000 erythrocytes, 16,700 leucocytes (lymphocytes, 3%; monocytes, 1%; polymorphonuclear leucocytes, 94%; eosinophils, 2%). The hemoglobin was 10.8 gm (74%).

Myringotomy of the right drum produced only a small amount of serosanguineous fluid. In the left ear a large amount of pus escaped through the incision. Cultures taken from the ear did not show growth after 24 hours. Penicillin, 60,000 units, was administered every three hours. On April 21st, the temperature decreased from 104° to 101° F., the pulse rate from 130 to 80. The white blood count was 13,050 (lymphocytes, 10%; monocytes, 2%; polymorphonuclear leucocytes, 88%). On April 22nd, the temperature varied between 100.4° and 102.8° F. and the pulse rate between 70 and 100. In the blood there were 3,770,000 erythrocytes and 9,250 leucocytes (lymphocytes, 20%; monocytes, 6%; polymorphonuclear leucocytes, 74%). Hemoglobin was 10.5 gm (72%). The patient's parents reported that they now noticed signs of aphasia; the child did not always understand what was said to her. She complained of severe headache in the left temporal area and the left ear was draining profusely. X-ray examination showed a diminished pneumatization of the left mastoid. Penicillin, 450,000 units, was given. On April 23rd, the temperature ranged between 100° and 102.4° F., and the pulse rate between 76 and 88. The aphasia persisted. Penicillin, 240,000 units, was given. On April 24th, the temperature varied between 98.6° and 100.4° F., and the pulse rate between 64 and 84. There were 7,250 leucocytes (lymphocytes, 30%; monocytes, 1%; polymorphonuclear leucocytes, 66%; eosinophils, 3%) in the blood. The child was rational. There was no prostration nor slow cerebration, but there was an amnesic aphasia and alexia. Eye grounds were normal. There was slight tenderness of the atlanto-

occipital membrane and both malar processes, but no tenderness of the eyeballs. There was no nystagmus. Abdominal reflexes were active; there was no dermatographism, no spastic symptoms, no positive Kernig's sign. There was paresis of the mouth branch of the right facial nerve. The heel-knee test could not be performed because the child did not understand what was wanted of her. There was no ataxia. The left ear, which had drained for three days, ceased discharging. The drum was gray except in the posterior and superior quadrant where it was red and bulging. There was no sagging of the superior and posterior wall of the external canal and no mastoid symptoms. The Weber test was not lateralized and the Rinne was negative on the left side. Examination of hearing for words could not be performed because she did not understand the words. Four drams of magnesium sulfate and 30,000 units of penicillin every three hours were given. On April 25th, the temperature ranged between 99° and 100° F. and the pulse rate between 64 and 80. The aphasia persisted. On April 26th at about 5:30 p. m., the child became comatose and two hours later she was operated upon. On the operating table she had a jacksonian attack with deviation of the eyes to the right, tonic and clonic convulsions of the right extremities and twitching of the right facial muscles. After the injection of curare and pentothal the convulsion ceased.

A retro-auricular incision was made on the left side. The mastoid contained small cells which were filled with granulations and, to a small extent, with mucopus. The dura of the middle fossa was exposed and found to be normal. The simple mastoid operation was completed. At the mastoid tip there were larger cells filled with mucopus. The antrum was filled with granulations but there was no frank pus. The insertion of the malar process contained small cells filled with mucopus. This and a part of the lateral wall of the antrum were removed. The horizontal semicircular canal and incus were found to be normal. The dura was exposed at the base and at the convexity of the temporal lobe. The dura was considerably bulging toward the antrum but there was no necrosis nor external pachymeningitis. A cross incision was made in the dura. The brain bulged markedly through the incision of the dura causing a primary herniation which was not as prominent as is seen in cases of deeply situated brain abscesses. The brain tissue was soft; the cortex, normal. Three punctures, 5 cm deep, were made. No pus escaped but edematous brain tissue blocked the cannula and the cortex was immediately changed into hemorrhagic tissue. Two more punctures likewise did not reveal pus at a depth of about 7 cm. The cannula entered the ventricle and clear cerebrospinal fluid escaped under normal pressure. Spinal puncture immediately after

the operation released about 2 cc of clear fluid under normal pressure. There were 7 cells per cmm in the fluid and Pandy's reaction was positive.

After the operation the temperature rose to 104° F. and the pulse rate to 160. On April 27th she was markedly improved. She appeared much brighter mentally and was able to repeat simple numbers and to make simple additions, but still showed inability to name objects. She slept a great deal. The temperature varied between 99.5° and 100.6° F. and the pulse rate between 86 and 96. There were 3,330,000 erythrocytes in the blood and 7,350 leucocytes (lymphocytes, 31%; polymorphonuclear leucocytes, 68%; eosinophils, 1%). The hemoglobin was 9.4 gm (65%). On April 28th, the child appeared slightly lethargic but still responded well. The temperature ranged between 98.6° and 100° F. and the pulse rate between 76 and 100. In the blood there were 3,490,000 erythrocytes and 12,500 leucocytes (lymphocytes, 31%; monocytes, 3%; polymorphonuclear leucocytes, 60%; eosinophils, 6%). The hemoglobin was 9.4 gm (65%). The wound was dry. There was no increase in the size of the herniation of the brain. After dressing, the child appeared brighter. She was given 100 cc of 50% dextrose. She could count and also read a few sentences. She was able to name a fountain-pen, telephone and glasses. On May 1st, the aphasia had almost disappeared. The brain herniation was granulating and did not show pulsations. On May 4th, the penicillin was discontinued. She was dismissed on May 11th.

Comment. In this case of a girl, aged 10 years, there was an acute otitis on the left side which, approximately in the second week, became associated with fever, chills, pain in the left temple, in the neck and in the left mastoid, with an increase of leucocytes and a decrease of lymphocytes, and, finally, with a jacksonian attack on the right side and unconsciousness. These symptoms, of course, indicate an intracranial complication and the question arises as to whether the complication had been otogenous in origin or not. A final answer is difficult because it has not been possible to prove the identity of the micro-organisms which caused the ear infection on the one hand, the intracranial complication on the other. Yet the otogenous origin can be assumed for the following reasons: (1) The complication became manifest after the onset of an acute otitis; (2) the cerebral symptoms indicated an involvement of the brain on the same side as the otitis; (3) the paracentesis proved that there was a retention of pus in the tympanic cavity. This would favor the development of intracranial complications. (4) Except for the otitis there was no other finding in the body to offer an etiology of

the brain involvement. These findings render the otogenous origin of the complication very likely, although not certain.

It is unusual that an acute otitis causes a complication in the second week. However, the findings of granulations in the mastoid and the course of the otitis which points to a probable pneumococcus Type III infection, indicate that the otitis dated further back than the parents reported.

A paracentesis was performed and high doses of penicillin were administered. This caused a decrease of fever, a decrease of leucocytes in the blood, and an increase of lymphocytes. Two days after admission there was intense pain in the left temple, a sensory aphasia and alexia, and four days after admission a jacksonian attack was noticed on the right side. At operation a subacute mastoiditis and edema of the brain were discovered, but there was no brain abscess. On the next day there was an improvement of the aphasia and five days after the operation the aphasia had almost, and the leucocytosis completely, disappeared. The child was cured.

CASE 2.—G. W., a white female aged 1½ years, had had a normal birth and had not suffered from any contagious diseases. For one year she suffered from an occasional recurrent otitis media. On April 19, 1944, the temperature rose to 105° F., the lips were cyanotic, the breathing irregular, and there was a twitching of the head. The right eardrum was bulging, the left drum was pinkish red. A myringotomy was performed on April 20th which released hemorrhagic fluid. There was no purulent secretion subsequent to the paracentesis. Sulfadiazine was given. On April 21st, the hemoglobin was 49.40%. There were 4,400,000 erythrocytes and 18,800 leucocytes (lymphocytes, 2%; polymorphonuclear leucocytes, 98%). On April 22nd, the hemoglobin was 51.89%; erythrocytes, 3,430,000; and leucocytes, 15,800 (lymphocytes, 38%; monocytes, 2%; polymorphonuclear leucocytes, 60%). On April 23rd, the hemoglobin was 51.89%; erythrocytes, 2,900,000; leucocytes, 11,500 (lymphocytes, 47%; polymorphonuclear leucocytes, 53%). The otitis subsided and the temperature became subfebrile. On April 26th, the temperature fell to 99° F., but the pulse rate rose to 140. There was restlessness, rigidity of the neck, a positive Kernig's sign and a paresis of the left arm. A transfusion of 275 cc of blood was made.

On April 27th, a simple mastoid operation was performed on both sides by another otologist. On the right side there were granulations and a small amount of pus in the mastoid. The hyperemic dura of the middle fossa was exposed. In the left mastoid there was a great amount of mucus and more bone was destroyed than on the

right side. On April 28th, the hemoglobin was 71.28%; erythrocytes, 4,000,000; leucocytes, 14,500. The temperature and pulse rate fell, but the decrease of temperature was more marked than the decrease of the pulse rate. The paresis of the left arm subsided, but there was an ataxia of both arms, and on one occasion, vomiting. On May 1st, the hemoglobin was 71.90%; erythrocytes, 4,300,000; leucocytes, 14,550 (lymphocytes, 35%; monocytes, 5%; polymorphonuclear leucocytes, 58%; eosinophils, 2%).

On admission on May 3rd, the temperature was 100.5° F. and the pulse rate 110. The child did not respond when called upon. There was a twitching of the body. If the child was lying quietly on her back, there was a slight conjugate deviation of the eyes to the left, but no nystagmus. The reaction of the pupils was normal. The nasolabial fold was less marked on the right side than on the left. There was a slight hyperesthesia of the skin, but no dermatographism. There was an auxiliary movement of the alae nasi in breathing. The child could not maintain the sitting position. The left arm was moved less frequently than the right but there was no paralysis of the left arm. There were rhythmical contractions of the muscles of the floor of the mouth resembling involuntary deglutition movements. It was not possible to examine the soft palate for similar contractions. In various intervals the child went suddenly into a marked opisthotonos and turned rapidly about the long axis of her body to the right. In this position she remained for several minutes. In the retro-auricular cavities there was mucus on both sides; the antrum was exposed. The eardrums on both sides had a dark blue color and the landmarks could not be determined. There was no discharge from the ears. The diagnosis of hematomypanum on both sides and of an inflammatory process in the posterior cranial fossa was made. On May 6th, all tests for tuberculosis were negative. The temperature rose to 101° F. and the pulse rate to 140. On May 8th, the spinal fluid and the eye grounds were found to be normal. On May 9th, the child responded to optic stimuli but not to acoustic stimuli. When pain stimuli were applied it distorted the face without expressing a sound. If the child was resting she moved her arm and leg on the right side more than on the left. If she became restless she grasped the right ear with the right hand. At the attempt to move the child's body she wept, but did not cry out. The turning convulsions of the body to the right were less frequent. If placed on the abdomen she could not turn back. The vertebral spine and atlanto-occipital membrane were not tender. Reflexes were normal. There was no deviation of the eyes and no nystagmus, but there were periodical rhythmical contractions of the muscles of the floor of the mouth. The tonsils

were hypertrophic. There was no dehydration and no drowsiness. If the child was lifted a marked opisthotonos was noticed. The diagnosis of a cerebellar abscess on the left side was made.

On May 10th, the temperature fell to 99° F. and the pulse rate rose to 160. On May 12th, both mastoids were re-opened. The left antrum and mastoid were filled with granulations. The sinus and dura of the posterior fossa were exposed and were found to be bulging into the mastoid cavity. There was a marked external pachymeningitis obscuring the boundaries of the sigmoid sinus. The dura of the middle fossa was normal. The superior angle of the petrous bone was removed and attempts were made to puncture the cerebellum. The attempts failed because the incision of the dura caused a severe hemorrhage originating probably in the sinus as well as in the granulations of the external pachymeningitis. On the right side the dura of the middle fossa was covered with granulations. The dura of the posterior fossa was found to be normal.

After the operation the temperature and the pulse rate fell gradually. On May 15th, the child was apparently well. She was lying on her left side, the head bent backwards. The child showed frequently shaking movements of the head and periodically turned the body to the left. On May 17th, the temperature and the pulse rate were normal. However, there was a slight hyperalgesia and a rigidity of the neck. She moved both arms but there was ataxia when she made an attempt to grasp something. The movements of the legs were normal. She sucked the fingers of the right hand, but never those of the left. Occasionally there was sighing and yawning but no vomiting.

On May 18th, a revision of the left mastoid was performed. The dura of the posterior fossa was covered by a layer of granulations, about 2 mm in thickness. The dura of the middle fossa was normal. The dura of the posterior fossa was exposed until about 2 cm beyond the posterior boundary of the mastoid when normal dura was reached. The sigmoid sinus did not show distinct margins, but after incision in the area of the sinus, blood spurted, probably from the sinus. A part of the occipital squama, the size of a quarter, was removed. A nick incision was made in the normal dura and the brain cannula was introduced about 3 cm deep. Punctures were performed in four directions but no pus was found. In the gaping nick incision the edematous arachnoid was bulging.

On May 20th, the patient was restless. There were clonic contractions of the left arm and blinking of the eyelids. The temperature was 99.8° F. and the pulse rate 120. In the next days a rapid improvement was noticed. The brain symptoms disappeared and

she was dismissed on May 25th. On May 30th, she could sit up without assistance. Occasionally there was sighing. A few days later she was completely well and in the following years her mental and physical development was entirely normal.

Comment. In this case of an infant there was a recurrent otitis media. During an acute attack, the otitis caused fever, disturbances of breathing and of blood circulation. A myringotomy was performed and sulfadiazine was administered. The otitis, the fever and the leucocytosis subsided. Six days after the myringotomy the pulse rate rose to 140 but the temperature remained at 99° F.; there were meningeal symptoms and a paresis of the left arm. A blood transfusion was made and a simple mastoid operation was performed on both sides. The extension of the infection in the mastoid was in accordance with the duration of the otitis. After the operation the acceleration of the pulse, the fever and the paresis of the left arm subsided; but seven days after the operation the fever returned. There was twitching of the head, a conjugate deviation of the eyes to the left, a slight paresis of the right facial nerve, a restriction of the movements of the left arm, rhythmical contractions of the muscles of the floor of the mouth, turning convulsions of the body to the right and opisthotonos. Otoscopy revealed a hematotympanum on both sides.

These symptoms indicated an involvement of the posterior cranial fossa. Among the neurological symptoms the turning convulsions of the body and the contractions of the muscles of the floor of the mouth are of particular interest.

According to Gerstmann⁹ there are in man three areas of the brain, the involvement of which may cause rotation about the long axis of the body: the parieto-occipital area, the crura cerebelli ad pontem and the cerebellum. The rotations caused by diseases of the cerebellum have been exhaustively studied.¹⁰ Gerstmann⁹ believes that in man the rotations of the body occur frequently in cerebellar diseases but are usually obscured by the ataxia and by the pronounced disturbances of the body equilibrium. In cerebellar abscesses the rotations were occasionally noticed, the direction being to the involved side or to the other side. It is certain that the rotations about the long axis of the body are a cerebellar symptom which, according to André-Thomas,¹¹ occurs particularly in lesions of the cerebellar vermis.

The contractions of the muscles of the floor of the mouth in Case 2 were not caused by an involvement of the hypoglossal nerve because the muscles of the tongue were found to be normal; these contractions were performed after the pattern of the muscular syn-

ergism, constituting the act of deglutition. Klien¹² has noticed continuous rhythmical contractions of the muscles of deglutition in three instances in which at autopsy cysts, subsequent to hemorrhages, have been found in identical parts of the cerebellar hemisphere. In the presented case the contractions were not continuous, they appeared rather in attacks; the soft palate was not examined for similar contractions. However, since in the presented case the neurological and surgical findings render the diagnosis of a cerebellar involvement certain, it is likely that, in agreement with the findings of Klien, the contractions of the floor of the mouth must be considered a cerebellar symptom.

The diagnosis of a complication in the posterior fossa being established, both mastoids were re-opened. On the left side an external pachymeningitis of the posterior fossa was discovered. Subsequent to the operation no improvement was noticed on neurological examination. The direction of the turning convulsions of the body changed to the left side. Six days after the operation, the dura of the left posterior fossa was re-exposed, the sinus was incised and a puncture of the cerebellum was performed. In the sinus there was blood; at the site of the cerebellar puncture the leptomeninges were found to be edematous but there was no cerebellar abscess. Rapid improvement ensued after this operation and resulted in a perfect and lasting cure.

As in Case 1 no bacteriological examination was performed to prove the otogenous origin of the brain complication. But again several findings render this origin likely: (1) There was a highly virulent ear infection which caused general vascular and respiratory troubles; (2) the brain complication made its appearance after the onset of the otitis; (3) so far as it was possible to determine, the neurological symptoms were found to be on the side of the more virulent otitis; (4) except for the otitis, there was no other finding to furnish an etiology of the brain involvement.

COMMENT

Taking it as granted that the intracranial complications in the presented cases are otitic in origin, the clinical symptoms point to an involvement of the brain and, to a lesser degree, to an involvement of the meninges. In Case 1 the left temporal lobe and, in Case 2 the cerebellum, has been involved. There has been no brain abscess in either case. At operation in the presented cases and in other cases of this type the findings were brain edema and eventually accumulation of fluid in the subarachnoid spaces. A hydrocephalus internus has never been proved in these instances, neither

at operation nor by means of encephalography. At operation the edema of the cerebellum is usually less marked than the edema of the temporal lobe, probably because the edematous cerebellum may expand toward the basilar cisternae or the foramen magnum whereas the edematous temporal lobe usually bulges through the surgical incision of the dura. In addition, experimental findings indicate that it is more difficult to produce an edema of the cerebellum than an edema of the cerebrum.

In favor of the diagnosis of brain edema are two additional findings which are frequently obtained in these cases: the success of the decompression of the brain and the rapid disappearance of the neurological symptoms subsequent to the operation. Local cerebral edema is associated with loss of function of the edematous area.¹³ If the edema resolves without having done permanent damage to the brain the function of the edematous area returns to normal. This is what happened in the presented cases and this likewise may happen in brain abscess, if the loss of cerebral function is caused by brain edema and not by the abscess per se.

Up to this point the diagnosis is based upon the facts. In an analysis of the etiology of the brain edema we must resort to hypotheses. Piquet¹⁴ believes that the brain edema originates in a localized meningitis which gives rise to an infection of the cerebral blood vessels. The infection extends to the walls of the third ventricle which is supposed to harbor a center, the involvement of which causes brain edema. This view does not seem to be very likely. If brain edema would be caused by a mechanism of this type it would frequently occur in purulent meningitis. There is, as a matter of fact, brain edema associated with purulent meningitis; yet it does not advance to the degree found in the presented cases in which the patients did not suffer from purulent meningitis.

Symonds^{6,7} believes that the otitic hydrocephalus is caused by an accumulation of fluid both within the ventricles and the sub-arachnoid spaces due to the defective absorption of spinal fluid through the arachnoid villi. This concept is apparently not quite in accordance with clinical facts. This I have commented upon elsewhere.¹

Borries²⁻⁵ claims that in the presented cases the underlying pathology is a nonpurulent otogenous encephalitis. It is very difficult to prove this hypothesis because these cases do not terminate fatally. Bijleveld¹⁵ and Kristensen¹⁶ performed an aspiration biopsy in instances of otogenous edema of the brain. In one case there were macrophages and lymphocytes surrounding a venule, in the other

there was brain edema and an "endovasculitis." Obviously findings of this type do not permit the diagnosis of nonpurulent encephalitis.

In order to substantiate the pathology of the supposed non-purulent encephalitis, Borries, Piquet and Minne^{17, 18} and others refer to patients who expired from an otogenous brain complication but did not show a brain abscess or a diffuse purulent leptomeningitis at autopsy. In instances of this type¹⁹⁻²¹ the findings are necroses, hemorrhages, perivascular infiltrations and eventually small multiple abscesses, but there are no large collections of pus. Disregarding the fact that several of these findings may have been caused by previous punctures of the brain, it is doubtful whether findings of this type are still consistent even with a broad concept of nonpurulent encephalitis. In the writer's opinion these findings indicate an acute brain abscess if they have a self-limiting course, or a phlegmonous encephalitis, if they take a spreading course. Inasmuch as several neuropathologists²² do not draw distinct boundaries between purulent and nonpurulent encephalitis, there may be, from the pathological point of view, a relationship between otogenous edema of the brain on one hand, acute brain abscess on the other hand. However, from the clinical point of view a distinction must be made. The acute brain abscess frequently terminates fatally despite decompression, brain puncture and, perhaps, chemotherapy, and the fatality is caused by an infection of the meninges and of the blood stream. In contradistinction, the otogenous edema of the brain may eventually cause blindness due to optic atrophy, but it is an exception rather than a rule that it terminates fatally and, if it does, the fatality is caused by increased brain pressure and not by an infection of the leptomeninges and the blood stream. For this reason, the otogenous edema of the brain can not be considered the forerunner of an acute or chronic brain abscess. It must be rather evaluated as a clinical entity, the pathology of which is not exactly known.

The following concept is an attempt to keep away from hypotheses as much as possible; it is not supposed to offer a final solution of the problem which would require a microscopic examination of the ear and brain in a case of this type. According to Roessle²³ serous inflammation is an attenuated inflammation; it is caused by an alteration of the permeability of the walls of the blood vessels allowing an outflow of albuminous fluid, poor in cells, from the blood vessels. An emigration of lymphocytes does take place but is usually obscured by the outflow of fluid. It is a fact that fluid of this type may enter cavities of the body, for example the spaces of the internal ear causing a serous labyrinthitis, or the subarachnoid spaces. Recently the opinion was advanced that this fluid may like-

wise penetrate into parenchymatous organs, i.e., into the liver or the brain. In fact, a serous inflammation of the brain is a common finding in the surrounding of a brain abscess and it is likewise not infrequent in pachymeningitis or in sinus thrombosis. In these instances toxins originating from the infected dura are supposed to be carried into the pial and cerebral blood vessels, increasing the permeability of the blood vessel walls and causing a serous meningitis or a brain edema, or both.¹ This is essentially the same mechanism which is supposed to be responsible for shock, in which substances absorbed from injured tissues may produce atonia and dilatation of the capillaries and venules, associated with an abnormal permeability to the body fluid, and edema of the tissues.²⁴ In sinus thrombosis brain edema is particularly frequent because in these instances the alteration of the permeability of the blood vessels is not only caused by the toxins but is additionally encouraged by the eventual impediment to the flow of the venous blood, due to the thrombosis of the sinus.¹ Usually the serous inflammation of the brain and the meninges does not cause marked clinical symptoms but in other instances, as in Case 2, it gives rise to alarming symptoms and, exceptionally, may even terminate fatally if the cerebral hypertension is not relieved by decompression.

The case of Schlender²⁵ offers the extremely rare opportunity to study the macroscopic changes of the brain in otogenous edema of the brain. For this reason a brief quotation of the case is pertinent. A child, aged 7 years, who had had several episodes of ear infections, suffered from a recurrent acute otitis on the right side for four days and on the left side for 24 hours, subsequent to a follicular angina. Two hours after admission the child became cyanotic, apathic, and there were jacksonian attacks on the left side, extending from the face toward the leg. No operation was performed. There was only slight fever. Four hours after admission the child expired. At autopsy there was a brain edema associated with a hyperemia of the brain and the meninges, and a flattening of the gyri. In the right middle cranial fossa there was a small extradural abscess, the size of a pea, containing streptococci. Corresponding to the extradural abscess there was a fibrinous exudate on the inside of the dura and the right temporal lobe was particularly edematous.

The case of Schlender proves that a serous inflammation of the brain and the meninges may occur in the presence of a minimal or even microscopic infection of the dura. Prados, Strowger and Feindel¹³ have shown that the brain of a cat responds even to a simple exposure to air with an alteration of the permeability and tonicity of the capillary endothelium causing diapedetic hemorrhages and brain edema. It seems a fair conclusion that, particularly in children, the

brain may respond in the same manner to toxins from an adjacent focus of infection, even if there is no gross infection of the dura.* It is likely that this has occurred in Case 1 presented here.

The exudate in serous inflammation may enter the brain, causing an inflammatory brain edema, or the spinal fluid within the subarachnoid spaces, causing a serous meningitis. Frequently both findings are associated. The reason for the accumulation of fluid either in the subarachnoid spaces or in the brain is not known. It is likewise not known for what reason the serous inflammation of the brain does not occur more frequently, advancing to the degree of causing clinical symptoms. But it is noteworthy that in experimental brain edema the degree of edema likewise varies from one experiment to the other, regardless of the method which has been employed to produce the edema. I have noticed this variability in my experiments²⁶ concerning the influence of x-rays upon the maturing brain and recently Prados, Strowger and Feindel¹³ have noticed it again in their experiments. Since apparently in man the exudate fails to extend through the ependyma of the ventricles and the epithelium of the choroid plexus, an internal hydrocephalus usually does not occur.

The serous exudate may cause damage to the brain tissue. Microscopic examination has revealed degenerative changes of the brain tissue and perivascular infiltration containing mononuclear cells, in instances of serous meningitis.^{27, 28} However, these changes do not advance to the formation of an acute brain abscess or a phlegmonous encephalitis, because otogenous edema of the brain either resolves or persists as such for a long period of time causing a cerebral hypertension which may eventually be fatal.²⁵

This concept does take in consideration the eventual occurrence of a nonpurulent encephalitis, in agreement with the concept of serous meningo-encephalitis of Koerner and Gruenberg.²⁹ Yet the surgical diagnosis of "brain edema" seems preferable because the term "nonpurulent encephalitis" implies a microscopic diagnosis which is not feasible in the majority of these instances.

Otogenous edema of the brain is supposed to present the clinical symptoms of an otogenous brain abscess.²⁻⁵ This would imply that otogenous edema of the brain has no symptomatology of its own. It is true that the diagnosis of otogenous edema of the brain is rarely made prior to the operation. It was not made in the presented cases. The reason is probably the comparatively infrequent

*Recently Pickles (New England J. Med. 240:192, 1949) has discovered an acute focal edema of the brain in children with head injuries.

occurrence of otogenous edema of the brain and the anxiety of the surgeon not to miss an eventual brain abscess. Yet the correct diagnosis can be eventually made although the differential diagnosis against brain abscess and serous meningitis, the inflammatory or hypertensive type,¹ is very difficult.

In this respect the following findings should be considered:

1. Brain edema occurs most frequently in children and young persons.
2. The patients are not acutely ill, there is no dehydration and no prostration.
3. At the onset there is usually fever, leucocytosis of the blood, and eventually chills.
4. There is headache which may fluctuate but there is no drowsiness and no slow cerebration except in children when they go through a protracted course of the illness or in patients who suffer from epileptical attacks. Piquet¹⁴ noticed a fluctuation of the intensity of drowsiness in these instances.
5. There may be venous engorgement of the retina but there is no marked degree of papilledema.
6. Pressure of spinal fluid is not raised or is slightly raised. (In hypertensive serous meningitis Garland and Seed³⁰ noticed an increase of pressure up to 950 mm, in the average more than 300 mm.) There may be a slight increase in cells and albumin.
7. Encephalography does not show changes in the ventricles.
8. "Irritative" brain symptoms, viz., jacksonian attacks, cerebellar fits, opisthotonos, lateral deviation of the eyes, twitching of the facial nerve, involuntary movements of the body, rotation of the body (Case 2), involuntary deglutition (Case 2) are common at the onset of the disease. Among 21 cases of serous inflammation of the brain and leptomeninges reported in the literature (including the two cases presented here and another of my cases reported by Dinolt³¹), "irritative" symptoms were noted in 11 cases. The "irritative" symptoms, when they occur at the onset of the disease, are of great importance for the diagnosis.
9. There is a great number of other neurological symptoms at the onset of otogenous edema of the brain: monoplegia, hemiplegia, facial paralysis, sensory aphasia, cerebellar symptoms, and eventually hemianopsia.
10. It seems that otogenous edema of the brain is particularly frequent in acute infections of the temporal bone, which is in agree-

ment with the findings of Richtner,³² but there are cases on record in which brain edema occurred in chronic otitis or subsequent to radical mastoid operations.

11. At operation the dura is found to be normal or there is a pachymeningitis. After incision of the dura the leptomeninges appear to be normal unless there is an association with serous meningitis. The cerebral cortex is slightly hyperemic and there is a moderate herniation of the brain subsequent to the incision of the dura. There is no discoloration of the cortex prior to a puncture. The puncture of the brain does not meet with the resistance of a capsule and does not release fluid of any kind unless the cannula enters the inferior horn. After decompression the brain herniation recedes rapidly.

The proper evaluation of these symptoms may permit to make the diagnosis of brain edema in a certain number of cases provided that the surgeon keeps in mind the eventuality of an otogenous edema of the brain. The writer feels that it may be less difficult to establish the differential diagnosis between brain edema and brain abscess than to distinguish between brain edema and serous meningitis, because in the latter case a distinction must be established between two different localizations of the same disease and not between two different morbid entities.

The treatment aims (1) at the removal of the focus of infection, (2) at decompression of the brain. To remove the focus of infection the different types of mastoid operations are employed. The dura should be exposed in all instances. So far as the decompression is concerned all depends on the condition of the patient as to whether surgery is immediately resorted to or conservative measures are applied.

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LETHAL GRANULOMATOUS ULCERATION INVOLVING
THE MIDLINE FACIAL TISSUES

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From time to time there has been presented before this society a group of granulomas having their primary site in the tissues of the nasal chambers or palate, usually running an indolent course for a year or two, sometimes even appearing to heal for a short time but again breaking down for no obvious cause. After a few months to a few years the lesion becomes more active and invades the neighboring bony structures, destroying the nose, palate and maxillary air sinuses, frequently with preservation of the upper lip, resulting in a shocking facial deformity. These patients die either from pure exhaustion or from hemorrhage.

The striking thing about these granulomas is the indolent but inveterate development of the lesions; where from their appearance we expect signs of active suppuration, none is present; the slow destructive advance suggests some sort of malignant lesion or blood dyscrasia. Histologic studies of the tissues of the lesion, of the blood and of the bone marrow have, however, failed to furnish any evidence to confirm this suspicion.

The pathologist studying sections of the diseased tissues appears to be struck by the absence of the usual signs of resistance to infection. Organisms which are found casually invading the tissues without the customary leukocytic barrier being set up do not appear to be the cause of the lesion. With the antibiotics of the present day such an organism may be completely eliminated from the tissues without affecting the progress of the disease. After stoppage of antibiotic treatment another different organism will appear invading the tissues in the same manner.

The bacteriologist and the mycologist have been unable to discover an etiologic agent. As their knowledge of possible causative organisms has increased and their technical skills at isolating possible

Read before the meeting of the American Laryngological Association, New York City, May 16-17, 1949.

invaders have improved and multiplied, they have carried efforts at isolating an etiologic factor to great lengths. Recently these efforts have included implanting material in the allantoid membrane of chick embryos but they have not revealed a causative micro-organism. For this reason the lesion has been termed "idiopathic" by some authors.

A typical pathologic description is that given by Hoover.¹ He stated: "On the border of the lesion is an amorphous mass of necrosis, beneath which there is an infiltration by inflammatory cells, chiefly lymphocytes and macrophages, with occasional plasma cells. A few polymorphonuclear leukocytes are also present. There is some new formation of capillaries. The larger vessels in the tissue show a definite perivascular cuff of lymphocytes and macrophages with degeneration of the arterial walls in some regions. While there are focal accumulations of the infiltrating cells in the tissues the lesion is not characteristic of tuberculosis, syphilis or leprosy. The diagnosis is that of a chronic granuloma of unknown cause." The pathologist added that the lesion suggested the Arthus phenomenon.

This lesion has received different names from different authors, being termed "granulomatous ulcer of the nose and face" by Hoover,¹ and "osteomyelitis necroticans faciei" by Rasmussen,² who concluded, after reviewing the literature and studying two cases of his own, that "the morbid process is assumed to be a disease sui generis." Lewy³ termed the condition, "gangrenous osteomyelitis of the paranasal sinuses;" Lierle,⁴ "chronic infectious ulcer of the nose;" Arrow-smith⁵ and Myerson,⁶ "gangosa" and Isbell,⁷ "chronic granulomatous ulcer of the nose of unknown cause."

The most vivid and accurate clinical description is that given by Stewart.⁸ If the term "midline of the face" is substituted for "nose" his title, "lethal granulomatous ulceration of the nose," seems most descriptive of the condition, and I feel should be accepted generally.

Stewart⁸ stated: "During the past ten years several cases of a peculiar type of ulceration of the nose, which correspond to no known pathologic entity, have come under our direct observation. The ulceration was progressive and invariably ended fatally."

Stewart⁸ divided the symptomatology of the disease into three stages, the first or prodromal stage, the second stage or period of active disease and the third or terminal stage.

The prodromal stage, Stewart⁸ pointed out, may last from a month or two to as long as four or five years. At first the patient

may merely be conscious of a stuffiness in the nose, sometimes accompanied by a watery or serosanguineous discharge. On the other hand the initial expression of the disease may be a superficial ulcer in the roof of the mouth or in the gingivobuccal groove. Some patients appear to have had infection in the paranasal sinuses preceding the onset of the first symptoms of lethal granuloma; in others a history or findings suggesting a preceding chronic infection of these structures cannot be obtained. A superficial ulceration of the septal mucosa, thought to be on a traumatic basis, may appear and disappear. If a submucous resection is done, a perforation usually will result.

The second stage, Stewart⁸ termed the period of active disease. The patient's nasal obstruction may be associated with a small brownish ulcer on the septum, inferior concha or roof of the mouth, covered with a gelatinous crust which on removal shows a shallow ulcerating surface. The discharge is purulent or sanguinopurulent and has a foul smell. The disease tends to spread from the palate to the inside of the nose and from the inside of the nose to the outside, so that early in the active stage the tip of the nose may become swollen and indurated. The disease progresses and sequestra of the nasal bones, the malar bones and the palatal bones may come away. Abscess formation may take place under the cheek and may require drainage. There may be a little fever with an irregular temperature and very moderate leukocytosis or even leukopenia. The polymorphonuclear leukocytes tend to maintain their normal proportions in the blood picture. Agranulocytosis has never been found and septicemia, as indicated by blood cultures, is absent. Except for a rather pronounced weakness and lassitude the patient may present a curious impression of well-being in spite of the serious appearance of the advancing lesion.

In the third or terminal stage Stewart⁸ stated that the obvious exhaustion of the patient is an outstanding clinical feature. The facial appearance is monstrous. The eyelids are swollen and purulent discharge trickles from between the lids. Sloughing areas appear over the lacrimal sacs and cheeks and the soft tissues about the external nose disappear, perhaps including the upper lip. The mutilating destruction may be extreme. The hard and soft palates may be completely destroyed. Through the large central aperture in the face, the tongue, the roof of the nose and the nasopharynx may be plainly visible, together with the roofs of the maxillary air sinuses exposed by ulcerative destruction of the lateral walls of the nose. The posterior pharyngeal wall may be covered with dirty gray necrotic material. The tongue remains unaffected and sequestration

of the basisphenoid has never been observed. The patient may die of hemorrhage from erosion of large vessels, which are troublesome to control in a necrotic region the bony walls of which have been destroyed. However, usually he appears to die from simple exhaustion.

Stewart⁸ summarized his clinical description by stating that the picture is one of progressive destruction of the nose, face and pharynx. The duration of the illness is from a few months to as long as five years. The most striking feature of the disease is the apparently complete absence of resistance on the part of the patient to the progress of the disease.

This vivid description of a baffling disorder can hardly be improved on.

In Hoover's extensive review¹ of the literature he was able to find approximately 60 cases of lethal granulomatous ulceration of the facial tissue including his own case. Rasmussen² in a later review was able to find only 33 cases which he felt were similar to his own. It is of course difficult to tell how many of the earlier cases might reveal a causative micro-organism if studied at the present time. Even now when we consider how few viruses may be present in a granuloma which they are causing, it is impossible to rule out absolutely the presence of this type of organism. Until such time as we can show definitely that such an organism is the etiologic factor, however, we must consider "lethal granulomatous ulceration of the midfacial tissues" an idiopathic disorder. As the name implies, this disorder has proved refractory to all treatments tried, although they have been many, varying from the use of iodides and mercury through roentgen therapy to the antibiotics.

From the purely clinical standpoint it seems apparent that there is nothing in the gross appearance of these "idiopathic" lesions to differentiate them from specific infectious granulomatous ulcerations occurring in the same locations. Clinicians experienced in observing gangosa feel certain that the case under consideration is an instance of this disorder. Indeed, except for the prognosis and the geographic area from which the patient comes, there is nothing to differentiate the two conditions. The controversy as to whether gangosa is an instance of tertiary syphilis, occurring in a particular race, need not be entered into here.⁹⁻¹¹ Yet clinicians experienced in observing the destructive lesions of tertiary syphilis about the face are certain the condition is syphilis and are amazed by the lack of confirmatory laboratory findings. The same thing holds true for those specializing in tuberculosis. They feel certain the lesion *must*

be tuberculous. Another will insist on blastomycosis or leprosy or oidiomycosis. Pathologists are careful to report sections taken from these lethal granulomas as being not "typical" or "diagnostic" of this or that condition, being prepared to admit that an atypical example of any one of the specific granulomas might be present.

In considering the reported cases and studying those encountered at the Mayo Clinic several pertinent questions arise. Is there a reason why the gross clinical pictures in the granulomas of unknown origin and in those of known origin are indistinguishable and why the histologic pictures in granulomas of whatever type have a basic identity with a by no means invariable modification produced by the etiologic agent? Why does the preferred site of the lesion appear to be the midline tissues of the face? Is there a reasonable hypothesis to explain the rare occurrence of these facial granulomas without an etiologic agent being demonstrable? What is the physiologic ^{Paradoxical} mechanism by which such a lesion can be produced? Why do patients with "idiopathic" granulomas show an almost complete lack of that physiologic activity known as resistance? Is there a single mechanism by which all these seemingly diverse phenomena could be produced? What therapeutic implications can be drawn from consideration of any possible causative factors that may be hypothesized?

Baker,¹² in discussing tissue changes in fungous diseases, found that, when they were tabulated in respect to the degree of suppuration, macrophage and giant-cell response, caseous necrosis and fibrosis, several of the deep fungous infections such as blastomycosis (North and South American), coccidioidomycosis, sporotrichosis and moniliasis showed all of these tissue changes. Others of the deep infections such as actinomycosis, nocardiosis and maduromycosis, showed all these changes except caseous necrosis. He felt that tissue changes in fungous infections represent response to proliferating and dying foreign bodies and in some instances may represent a hypersensitivity to the presence of an endotoxin. It would seem evident from this report of Baker that in fungous infections at least the body is reacting in a stereotyped manner to the whole group of fungi although some relatively unimportant modifications are produced by the specific organism. To put it in another way, resistance to such organisms uses the same immunologic mechanism in each instance.

It might be enlightening to list under the causative organism involved the various ulcerating lesions of the facial tissues from which it has been suggested that lethal granulomatous ulceration must be differentiated. They are: 1. *Bacillaceae*: A. Anthrax. Jordan and Burrows¹³ pointed out that *Bacillus anthracis* is the only member of

that large group pathogenic for man; 2. *Parvobacteriaceae*: A. Glanders; 3. *Mycobacteriaceae*: A. Tuberculosis; B. Leprosy; 4. *Fungi*: A. European blastomycosis (torulosis); B. American blastomycosis (oidiomycosis); C. Coccidioidomycosis (valley fever); D. Rhinosporidiosis; 5. *Treponemataceae*: A. Syphilis; B. Yaws, and 6. *Protozoa*: A. Leishmaniasis.

It is immediately apparent that diseases caused by the Eubacteriales, the organisms most commonly thought of in the infections which we meet in the human, are not included in this list. Even with the Eubacteriales it is only in response to those members of the group actively producing toxin that suppurative inflammation results.¹⁴ Bacterins or bacterial proteins produce antibodies of a feeble reactivity in so far as humoral antibodies are concerned.¹⁵ The character which all the organisms enumerated hold in common is the fact that they are slow or meager producers of exotoxin (or simply toxin).

In responding to the environmental stress produced by invasion by micro-organisms, Forbus¹⁴ stated, the body makes use of two stereotyped defense mechanisms, suppurative and granulomatous inflammation. In the first the responding cell is the polymorphonuclear leukocyte; in the second, the cells of the reticulo-endothelial system, especially the macrophage. He found that both suppurative and granulomatous inflammation may be either acute or chronic. A third type of inflammation, which he characterized as being a mixture of the other two, also exists.

The cells of the reticulo-endothelial system in granulomatous inflammation undergo many successive morphologic changes. These are proliferation, degeneration, death and dissolution, phagocytosis, mobilization and antibody production. In terms of the biologic properties of the reticulo-endothelial cells the proliferative reaction is at times so enormous that the lesions often appear to the clinician and even to the pathologist as tumors. This is responsible for the term "granuloma," introduced when the distinctions between hyperplasia and neoplasia could not be so sharply drawn as they are today. The proliferative features of granulomatous inflammatory disease are often so prominent that the clinical observer is overimpressed by these purely secondary features of the disease. These cells that become so abundant must eventually disappear unless the inflammatory reaction is ineffective and the patient dies. Thus necrosis of the reacting cells is characteristic of granulomatous inflammation. Two types of necrosis occur: coagulation necrosis as may be seen in the healed and healing stages of Hodgkin's disease, and liquefaction

necrosis which is present in those granulomas having the same clinical appearance as the idiopathic type. Characteristic of the granulomas is the fact that differential blood counts have a very limited usefulness indeed in the diagnosis of granulomatous inflammation. In spite of the fact that the reacting cells in granulomas multiply continuously, paradoxically, leukopenia rather than the expected leukocytosis is common. The relative mononucleosis which occasionally may be found constitutes an unfavorable rather than a favorable prognostic sign.

Specific sensitization of the skin is a characteristic feature of some of the granulomatous infectious diseases. Prominent among this group are tuberculosis, brucellosis, tularemia, typhoid fever, coccidioidomycosis, venereal lymphogranuloma and histoplasmosis. The production of so-called sensitizing antibody may be a feature of granulomatous inflammation, but a typical granuloma may evolve without it. Other forms of immune bodies may also be present in these infections. Neutralizing antibodies are conspicuous in the viral and rickettsial diseases; complement-fixing antibody develops in highly significant quantity in syphilis, in coccidioidomycosis and in certain of the parasitic granulomatous infections. Opsonins and agglutinins as well as precipitins appear in important quantities in brucellosis, typhoid fever and certain other bacterial granulomatous inflammations. The presence of antibodies in the blood serum is not necessary, however, for the development of typical granuloma but tends to suggest a mixed inflammation. Forbus¹⁴ stated that the etiologic diagnosis of inflammatory granulomatous disease presents very great difficulty. From biopsy of the specimen it may be only possible to say that it is a pure granuloma or a necrotizing granuloma.

Ross¹⁶ showed that on injection of staphylococcus toxin into immunized rabbits either a suppurative or a granulomatous inflammation could be produced, depending on the dilution of the toxin; relatively strong toxin produced a suppurative inflammation and relatively weak toxin a granulomatous reaction. There was no sharp demarcation or division between the two reactions, there being a midarea where the reaction partook of both processes.

After intradermal injections of living *Staphylococcus aureus* into normal animals Cannon and Pacheco¹⁷ found edema of the subcutis with infiltration largely by polymorphonuclear leukocytes. The reaction in skin previously immunized by intradermal injections of killed *Staphylococcus aureus* was found markedly different. At an early stage there was an enormous infiltration, mostly of lymph-

ocytes and monocytes, in the subcutis. They tended to become massed around a region of marked bacterial concentration, and here there were many evidences of necrosis of the cells of inflammation with accompanying hemorrhage and even thrombosis of the capillaries. These findings suggest that whether the invading micro-organism is a toxin producer or not influences strongly the type of cellular defense elicited, and at the same time indicates that in an immunized animal it will require a greater concentration of toxin to produce a polymorphonuclear leukocytic response.

The findings of Cannon and Pacheco¹⁷ may be compared to those of Arkin¹⁸ in periarteritis nodosa, which will be shown later to be a reaction form closely related to granuloma. Arkin divided periarteritis nodosa into four stages. In describing the acute inflammatory stage he noted an infiltration of the media and adventitia of the vessels with polymorphonuclear neutrophils and sometimes also eosinophils, lymphocytes and plasma cells. In the granulomatous stage he found a marked proliferation of fibroblasts from the adventitia into the inflammatory zone accompanied by a reduction of the polymorphonuclear leukocytes with an increase of the lymphocytes and plasma cells. The histologic picture described by Arkin¹⁸ in cases of periarteritis nodosa is strikingly like that described by Cannon and Pacheco¹⁷ in their studies of the cellular reactions of the skin of the guinea pig, first in the normal animal and then the animal as influenced by local active immunization to intradermal injections of living *Staphylococcus aureus*.

It would seem to be a reasonable conclusion that the acute inflammatory stage of Arkin¹⁸ takes place before local tissue immunity has reached marked development. After local tissue immunity has reached a high degree the cellular reaction resembles that found by Cannon and Pacheco¹⁷ on injecting *Staphylococcus aureus* into local areas which had been actively immunized.

Arthus and Breton¹⁹ demonstrated that if an area of skin is sensitized and then antigen is injected into the area a pathologic picture similar to that produced in granuloma will result. Opie²⁰ observed that when foreign proteins are injected intradermally into rabbits much of the material is quickly demonstrable in the blood stream, but with repeated injection of the antigen the quantity of foreign protein that enters the blood stream diminishes, and finally with advanced immunization none enters unless massive doses have been employed. Furthermore, in the immunized animal the foreign protein is fixed at the site of injection, a fact that Opie felt to be of significance because it was in the immunized area that "anaphylactic"

inflammation occurred. This anaphylactic inflammation histologically appears to be indistinguishable from that encountered in pure granulomatous inflammation or from that produced by Cannon and Pacheco¹⁷ by injecting staphylococci into an immunized area of skin.

If this reaction be anaphylactic or allergic, how can it be seen occurring as a part of a normal resistance mechanism such as granulomatous inflammation? If this be the case, "allergy" will have to be redefined to include normal as well as altered reaction. Opie²⁰ expressed the opinion that since a similar reaction occurs when antigen and antibody are simultaneously injected into the tissues of a normal animal but not when antigen and normal serum are injected, and since the same effect is observed when antigen is injected into the tissues of a sensitized animal, anaphylactic inflammation occurs when antigen and antibody have met in the tissues.

The only difference between the histologic lesion in the specific granulomatous inflammations, idiopathic granulomatous inflammations and the phenomenon produced in the laboratory and called the Arthus phenomenon is lack of knowledge as to the cause in idiopathic granuloma. In the first, when local tissue immunity is established, a pure granuloma results with or without pronounced central necrosis, depending on the organism involved, or a granuloma of the mixed type results if the organism is capable of some toxin production. In the third the injection of bacterial protein or bacterin which is known to be feebly toxic produces the reaction. The idiopathic granuloma occurs under natural conditions and yet no organism or other source from which nontoxic protein material might be derived has been identified. In this instance only there may be dysfunction (altered reactivity) of some part of the immune mechanism, and logically therefore only an idiopathic granuloma might be termed an allergy.

From the evidence so far presented it would seem that specific granuloma formation with ulceration, if it is near a skin surface, is a normal defense mechanism and should not be termed an allergy, bacterial or otherwise. In the nonspecific or idiopathic granulomas, however, the case is quite different. We have a lesion presenting the clinical and pathologic appearance of a granuloma, in other words, the normal defense mechanism of granulomatous inflammation, but without being able to discover a normal stimulus to initiate such a reaction. The idiopathic granuloma may therefore be considered an abnormal reaction and therefore an allergy. To settle this point it would seem to be necessary to inquire into what is allergy and what is its fundamental pathology.

I shall first outline a hypothesis for allergy that seems to fit all the known facts and yet avoids the paradoxes that had made the subject of allergy and immunology so difficult for me.

ALLERGY

I have found the problems of allergy much less difficult of solution since setting up for myself the following schema.

1. The diagnosis of allergy is primarily clinical. It is on the gross and microscopic appearance of the lesions, not primarily on the basis of immune reactions and hematologic studies, that the diagnosis is made.

2. Allergy is primarily a vasculitis; secondary necrosis, hyaline change and fibrosis are confusing elements in the picture introduced by the attempts of the body to heal the lesion.

3. The vasculitis tends to be focal in character, sometimes involving an entire organ but usually affecting more or less isolated areas (the shock organ).

4. The vasculitis is produced as a result of cell injury that sets free substances such as histamine or the "H substance" suggested by Lewis and co-workers²¹⁻²³ or antibody-like substances such as the "necrosin" associated with gamma globulin found by Menkin.²⁴

5. The cell injury may take place as a result of an antigen-antibody reaction within the cell or at the cell membrane as suggested by Opie,²⁰ or it may result from localized vascular spasm causing anoxic conditions in certain areas of tissues which secondarily produce the cell injury resulting in the release of toxic products, as suggested by Müller²⁵ and Parrisius.²⁶ Thus clinical appearances typical of allergy may manifest themselves without the intervention of an antigen-antibody type of mechanism.

6. Allergy can be considered as three related but not identical physiologic mechanisms. These mechanisms are to be considered perversions of three normal resistance mechanisms. Considered in the order of their probable phylogenetic and pathogenetic priority they are:

- A. *Physical Allergy.* In this condition physical agents such as cold, heat, fatigue and emotional perturbations produce localized areas of vascular spasms with resulting anoxia, cellular injury and localized vasculitis as demonstrated by Müller²⁷ and by Brown.²⁸ Its "immunologic" prototype is that of "homeostasis" as described by Cannon,²⁹ by which the body adjusts itself to changes in its internal and external environment produced by physical agents.

B. Bacterial Allergy or Tissue Allergy. Focal hyperimmune areas, as suggested by Kahn,¹⁵ attract circulating antigen with resulting cellular injury and vasculitis, producing the clinical picture of allergy. The immunologic prototype is granulomatous inflammation which develops in response to invasion by micro-organisms which are slow or meager producers of toxin.

C. Humoral Allergy. In this form we find the "sensitizing antibody," "blocking antibody," "opsonins," "agglutinins" and the like which appear to be associated with gamma globulin appearing in solution in the blood serum. In this type of allergy sudden, rapid junction of antigen and antibody at the cell membrane or within the cell produces cell injury with the release of toxic products. The vasculitis produced is not so severe as in tissue or bacterial allergy, a fact that suggests that the circulating antibody may have a buffering action and that less toxin is released from tissue cells by reaction. The local allergic lesion has the general appearance of the allergic wheal. Its immunologic prototype is suppurative inflammation with a polymorphonuclear cellular response to invasion by micro-organisms which are potent producers of "exotoxin."

There is nothing in this hypothesis to suggest that these three types of allergy are mutually exclusive; indeed, clinically I feel that they are frequently found occurring in association.

I have found that if one excludes pollinosis and inhalant allergies not more than 10% of allergic patients will be found to give specifically significant cutaneous reactions. In otology and rhinology we are dealing largely with the nonreacting 90%. It should not be surprising, therefore, that our therapeutic efforts directed toward relieving a humoral allergy that is not there should have yielded so little in clinical results. This concept that I have presented vastly broadens the field of therapeutic possibility and has given me considerable success in dealing with previously refractory problems.

Kahn¹⁵ found it unnecessary to conceive that the tissue cells in allergy in man produce "sensitizing" antibodies aimed presumably to render themselves hypersensitive to some antigen or allergen. It seemed to him more reasonable to assume that the antibody produced by an allergic person toward an allergen is essentially not different from the antibody produced toward an antigen or micro-organism. The outstanding disturbance in the allergic person is that his tissue cells respond immunologically to substances that are not antigenic to normal persons; his tissue cells are immunologically hyperactive. He may react immunologically to drugs or other organic substances and also to inorganic substances; he may react on first contact with

an allergic agent in the absence of an incubation period; he may react nonspecifically and most frequently he will give maximal reactions to minimal doses of the allergen.

While Kahn's contribution¹⁵ of the concept of tissue immunity furnishes the key to the puzzle of allergy, the contributions of Müller,²⁵ Petersen³⁰ and Selye³¹ must also be considered fundamental in the formulation of the concept that I have presented.

I shall review a little of the pertinent literature in regard to this concept of allergy and attempt to show how it connects with the problem of idiopathic granulomatous ulceration under discussion.

In discussing the nature of allergy Rackemann³² stated that the fact that the symptoms of allergy depend on a characteristic and uniform pathologic condition is important. Spasm of smooth muscle, stimulation of glands and increased permeability of capillaries are produced with such regularity as to justify the concept of a common end product which results from a great number of reactions. He quoted Lewis to the effect that cellular injury results in the liberation of those histamine-like substances which are normal constituents of the cell contents.

In immunity, according to Rackemann,³² no reaction occurs because the antibodies are predominantly in the circulating blood where they can destroy or modify the antigen before it can make contact with the cells. In the normal person no reaction occurs because there are no antibodies. However, a dose of serum or any foreign substance induces the formation of antibodies which may develop to such concentration as to react with the *remains* of antigen and precipitate a reaction called serum disease. It should be emphasized that serum disease is a normal response of a normal person. Furthermore the differences between this normal response with its ten-day incubation period and acute shock occurring within a few minutes are quantitative rather than qualitative. Antibodies may be many or few; they may be attached to cells or occur free in the blood, or they may be in both situations at the same time. The differences are of degree rather than of kind. Rackemann³² pointed out that the production of antibodies in general is a normal function, that allergy is a normal function and that allergy is a reaction which is characterized by the easy formation of cellular antibodies in great abundance. An individual may be considered allergic in the sense that he has an easy tendency to develop hypersensitiveness. In this discussion Rackemann³² is in agreement with the hypothesis presented in earlier paragraphs, up to a certain point. He states that allergy may result from a great variety of reactions, quotes Lewis

to the effect that cellular injury releasing toxic substances from the cell produces the vascular effect resulting in the clinical picture of allergy, yet appears to insist that the only mechanism by which injury to cells can be produced is by the union of antigen and antibody within the cell or at least at the cell membrane. He does, however, appear to be receptive toward the concept that allergy is a normal, not an abnormal mechanism.

Burnet³³ appeared to advance even further toward this position. He stated that the changes which occur in an organism in response to an infection usually enable it to throw off the infection and are thus beneficial. Noninfectious dead micro-organisms may also provoke alteration, and apparently harmless substances may occasionally cause alterations in the tissues or in the circulatory apparatus. He suggested that the basic mechanism consists in the recognition by the tissues of the organism of the difference between "self" and "not self." Identical defense measures in the case of harmless substances such as ragweed pollen may set up a mode of reaction which is actually deleterious to the organism. He can only suppose that on the whole the benefit outweighs the harm, or otherwise the device of immunity-sensitization would not have survived the long course of evolution. All these authors insist, however, that allergy, hypersensitiveness, anaphylaxis and so on are associated with the presence of circulating antibodies.

German immunologists under the leadership of Ehrlich, Pfeiffer and others, being more concerned with the relationship between immunity and serum antibodies, have made us somewhat forgetful of the work of Metchnikoff and his colleagues at the Pasteur Institute who stressed the importance of phagocytosis as a mechanism in immunity.³⁴ These different approaches to the problem of the resistance of the body to invasion by bacteria led to two concepts of the mechanism involved, the "humoral theory" and the so-called cellular theory of immunity. The belief of Metchnikoff that antibody and complement are derived from leukocytes has received confirmation from recent workers such as Chase, White and Dougherty³⁵ and others³⁶ who have presented convincing evidence that the soluble gamma euglobulin which forms the circulating antibodies comes from the reticulo-endothelial system and probably from the lymphocytes.

Cannon and Pacheco¹⁷ stated that the relatively unsatisfactory results of many years' emphasis on humoral factors in the defense against infectious disease had led to a re-examination of some of the underlying mechanisms involved, and as a result the cellular reac-

tions of immunity were receiving more attention. They stated that accumulating evidence pointed to a close relationship between phagocytic cells, particularly macrophages, and antibody formation. They suggested the concept that antibodies may be merely excess products resulting from ingestion of antigenic substances by phagocytes. Serums or solutions of antibodies may be simply by-products, the fundamental reactions actually occurring within the phagocytic cells. They added that the ability of micro-organisms to adapt, multiply and disseminate may be prevented by the defense mechanisms of the body. These may be both cellular and humoral. The early mobilization of phagocytic cells at the site of bacterial infection may serve to restrain the rapid increase in numbers of bacteria and the rate of engulfment by macrophages may exceed the rate of multiplication of the bacteria. Localization of the organism by mechanical factors such as lymphatic blockade and an antigen-antibody reaction in the tissues may result in the formation of chemotactic substances which quickly lead to a pronounced infiltration by cells of inflammation which are quantitatively and qualitatively different from those responding in the normal animal. In active inflammation it is probable that a summation of all these forces, specific as well as nonspecific, ensures an effective resistance against extension of infection.

The concept of tissue immunity (the third type of immunity) has been extended and developed by Kahn,¹⁵ who has in particular called attention to the defensive properties of the skin and subcutaneous tissues. Kahn stated: "The immunologic significance of the anchoring capability of the cutaneous tissues for micro-organisms and antigen is clear. The cutaneous tissue not only stands guard in preventing micro-organisms and antigens from boring through into the deeper tissues from without but by anchoring micro-organisms and antigens from within, the same tissue aids the body in eliminating them outwardly. This anchoring capability is not limited to the outer layers of the cutaneous tissue but is manifested also by the subcutaneous tissue. When an antigenic agent is injected into the cutaneous tissue of an immunized individual, it is anchored locally and is circumscribed by an inflammatory reaction. When the same antigenic agent is circulating in the blood stream of an immunized individual, it may similarly be anchored in given areas of the cutaneous tissue and be circumscribed by inflammatory reactions."

Kahn¹⁵ stated that it is reasonable to believe that the injections of foreign protein have similar immunologic effects on a host whether the protein comes from milk, serum, pollens or micro-organisms. He did not feel that it was necessary to call upon the concept of tissue

hypersensitiveness to interpret the results observed following the injections of protein into an animal. One can understand, he said, why Richet created the term "anaphylaxis" when he saw an animal die following a second injection of protein directly into the blood stream, and why Arthus believed that he dealt with a condition of local anaphylaxis when he saw local inflammation following a second injection of an antigen given subcutaneously. Such unusual reactions of animals to a second injection, Kahn believed, are readily explicable by assuming not that the tissues have become hypersensitive but that they have become hyperimmune.

Kahn¹⁵ pointed out that studies of the defensive capabilities of antibodies and phagocytes have laid the foundation of present-day immunology, but while these studies have been fruitful in coping with toxin-producing micro-organisms and have thrown light on the role of mobile and fixed phagocytes in infections, as far as the role of the tissues, the very seat of infection, is concerned, little is known. Indeed the mechanism of defense against those micro-organisms which are slow or meager toxin producers and the part played in this defense not only by the tissues but also by the antibodies are as yet an open field for investigation. Studies on tissue immunity, Kahn believed, should also throw light on responses to parasites larger than bacteria. In many cases of parasitism we are dealing with tissue reactions with little indication of any humoral reactions. The mechanism of the tissue reactions to parasites may not differ markedly from the mechanism of these reactions to bacteria and indeed to proteins. Kahn reviewed the development of the concept of tissue hypersensitiveness and called attention to the fact that the earlier workers such as Richet, Arthus and Breton¹⁰ and von Pirquet³⁷ combined the phenomenon of local hypersensitiveness or local anaphylaxis with the phenomenon of general anaphylaxis into the concept of "allergy." On the basis of these considerations the sensitized state is generally defined as a condition in which an animal is in some way antagonistic to its own defenses against specific micro-organisms or other antigenic agents. Kahn found himself at a loss to fit this concept of allergy into the scheme of immunity. As an adherent of the "unitarian hypothesis" he believed that precipitins, agglutinins and bacteriolysins represent one type of antibody reacting under different physicochemical conditions. He did not see how it was possible therefore for the same antibody to protect the host under one set of conditions and act as a "sensitizing antibody" under another. He pointed out that many authors regarded allergy as a basically defensive condition by which vital organs were protected at the expense of local injury.

X In considering the problems of immunity and allergy from the phylogenetic standpoint, Kahn¹⁵ felt that the defensive mechanisms which a host has developed through evolutionary ages form the bases for the mechanisms he utilizes in freeing himself of protein and other harmless antigens when they are introduced into his tissues. He felt that this view of the relationship between the immunologic responses to micro-organisms under natural conditions and the response to nontoxic antigens under experimental conditions will help greatly in understanding many of the reactions observed in immunity. Kahn felt that in immunity as in other physiologic functions of higher animals, while certain cells have the function of protecting the entire animal against pathogenic micro-organisms, these cells do not carry the entire burden of defense. Rather all cells possess immunologic capabilities to some degree, and it is unnecessary to assume a complete loss of defensive function by all but a certain specialized group of cells, as do the proponents of the concept of humoral immunity. In the struggle for survival the capacity to react against micro-organisms has become inherent in the tissue cells with the result that whenever the tissues come in contact with harmless antigenic material they react as though they were in contact with micro-organisms. This would serve to explain why the same fundamental pathologic picture can be produced by certain micro-organisms and by the injection of nontoxic foreign protein indifferently. It is to be noted that the organisms producing these reactions under natural conditions usually are of the type that are "slow or meager toxin producers."

X Kahn¹⁵ noted that two types of tissue changes can be differentiated as a result of immunization. Interpreted in terms of immune globulin formed by the cells, two types of immune globulin are noted. One type may be looked on as insoluble because it can not be washed away from the cells by surrounding fluids. The other type of immune globulin may be looked on as soluble because it can be washed away from the cells by the surrounding fluids. The former immune globulin is an inseparable part of the cell structure while the latter, finding its way into the fluids of the body, becomes the circulating antibody. Since it would appear that circulating antibodies occur largely in response to toxins and since most of the micro-organisms do not produce a large quantity of soluble toxin, Kahn¹⁵ would seem to imply by this statement that most immunity is not primarily associated with circulating antibody.

+ He also found that anchoring of micro-organisms and other antigens is the outstanding defense in the immune state. He felt that the widespread prevalence of micro-organisms wherever life

exists, and their constant contact with the surface tissues of animals, have produced the localizing mechanisms which are the first step in an elaborate tissue reaction aimed not merely to prevent micro-organisms from invading the body but also to destroy them locally in the area in which they happen to gain entrance. That this anchoring capability should be especially marked in the case of surface tissues can readily be understood. Tissue necrosis in pre-existing inflammatory tissue-antigen reactions Kahn¹⁵ found to be a common immunologic phenomenon. He pointed out that it is seen clinically under natural conditions of infection when the wall which has kept micro-organisms localized in a given focus breaks down, resulting in their escape into the blood stream with a flaring up and necrosis in other pre-existing foci for which cells have become hyperimmunized.

Kahn¹⁵ emphasized, however, that he believed tissue necrosis taking place within an inflammatory area to be a phenomenon which is opposed to the phenomenon of inflammation. The latter phenomenon is a manifestation of a host against a parasite or antigen while the phenomenon of tissue necrosis, he stated, is a manifestation of a parasite or antigen against the tissues of the host. When an immunized tissue localizes a bacterial antigen, injury to the tissues will produce an inflammatory reaction. If, however, an excess of antigen is present in the localized area, according to Kahn,¹⁵ necrosis will result by an unknown mechanism which he suggested may be blocking of the capillaries by excess antigen.

The disturbances known as allergy in man Kahn believed to be various manifestations of specific hyperimmunity, and he found hyperactivity of a physiologic function to be a common biologic phenomenon. The responses of the allergic person to a particular allergen do not obey the general laws of immunity. In an unimmunized animal only a dose of antigen of a given size will call forth inflammation in the local tissue and a relatively large quantity of the antigen must be present in the blood stream before tissue necrosis in the inflammatory area will become evident. In the allergic person minute doses of the allergen will call forth these phenomena, often nonspecifically.

However, Kahn¹⁵ pointed out the marked difference existing between bacterial and nonbacterial protein as antigen. Taking as an illustration the phenomenon of tissue necrosis in preformed inflammatory areas as exhibited by bacterial-immunized and by protein-immunized animals Kahn found that only an animal in a high state of immunity will exhibit this latter phenomenon, while to a substance such as typhoid vaccine an animal may exhibit necrosis al-

though it may never have received an immunizing injection of this vaccine. It would thus seem evident that the natural immunity to the constituents of the typhoid bacilli corresponds to a marked immunity to a nonbacterial protein and not to a mild immunity to this protein. Kahn did not feel that Pfeiffer's concept that typhoid bacilli contain an endotoxin conforms to newer knowledge. The relatively marked local reactions manifested by man to the injection of typhoid vaccine in the skin and the similarly marked systemic reactions when the vaccine is injected intravenously are due to the immunity possessed by man to the typhoid bacilli and their constituents, and not in his opinion to any endotoxin contained in the bodies of the bacilli.

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Kahn¹⁵ divided infectious diseases broadly into three classes: those in which nontoxic antigenic constituents of the micro-organisms play the outstanding roles, those in which toxins of micro-organisms play the outstanding roles and those in which both toxic and nontoxic agents play the outstanding roles in producing the immune responses. It is known that nontoxic protein antigens are capable of producing injury and necrosis of tissue in immunized animals. The phenomenon of tissue necrosis in preformed inflammatory areas is manifested to protein antigens. He believed, therefore, that an infectious disease due to micro-organisms free from exotoxin or endotoxin is entirely possible. He suggested that if we considered a hypothetical infection in which micro-organisms free from toxin play the outstanding role, we would note that any localization of the micro-organisms in a tissue would also lead to local injury followed by inflammation. The host may have been able to bacteriolysis the attacking micro-organisms but this may not mean that he has been able to destroy the liberated constituents of the micro-organisms. Suppose as some protein constituents are circulating in the blood stream and are taken up by the tissues they remain localized in a certain tissue owing to the inability of this tissue to proteolyze them. Kahn had seen repeated instances of the localization of antigen in the tissues of an immunized host in the absence of the capability of such tissue to destroy it. As time goes on, he supposed, the patient becomes re-infected with similar micro-organisms. Recalling the phenomenon of tissue necrosis in pre-existing inflammatory areas we might expect the appearance of a granuloma with central necrosis in such an area of tissue.

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Kahn¹⁵ pointed out that keeping in mind the complexity of infective processes in which nontoxic bacterial constituents act as antigens, a single abnormality in the immunologic chain which might interfere with the bacteriolysis of the micro-organisms, with the pro-

teolysis of the protein constituents or with the destruction of all other antigenic constituents may lead to tissue disturbances. It must also be kept in mind, he said, that the phenomenon of tissue necrosis may manifest itself only to a slight degree, resulting in minor tissue disturbances. Hence any localization of a nontoxic antigen in a tissue which might be insufficient to produce noticeable disturbance under ordinary circumstances might give indications of disturbance when the same or some similar antigen is circulating in the blood stream, since this circulatory antigen would also tend to accumulate in the same tissue. He was inclined to believe that when we meet with disturbances that tend to come and go, the causative agent is a nontoxic antigen, and the flare-up represents in most instances a manifestation of the phenomenon of tissue necrosis in preformed inflammatory areas.

Kahn¹⁵ here presented a hypothetical case which almost exactly fits the findings in a lethal granulomatous ulceration in the midline tissues of the face. Through previous infections these naturally reactive tissues might have become hyperimmunized or might still retain nontoxic antigen. Tissue necrosis might then ensue from any specific or nonspecific nontoxic antigen circulating in the blood, possibly even from absorption of "anaphylactogens" through the intestinal wall. The hypothesis would also serve to explain the fundamental histologic identity of the process with granulomas in the same area caused by any of the micro-organisms which are meager toxin producers.

Although the concept of tissue immunity as outlined by Kahn¹⁵ is not accepted by all immunologists, its development appears to have been made along logical lines and it integrates and makes understandable much that is admittedly confusing when the process is considered along the lines of immunity versus hypersensitivity or allergy. In addition, since 1936 when Kahn's book, "Tissue Immunity," was published, no evidence appears to have been produced which would indicate his hypothesis to be incorrect. In discussing "Immunity Versus Hypersensitivity" Boyd³⁸ gave no better explanation than that of Burnet³³ already mentioned in this paper. Boyd³⁸ himself stated, "Possibly almost any kind of body cell can produce some antibodies for local concentrations have been observed." According to Landsteiner,³⁹ findings which suggest the possibility of local antibody formation in infected sites have been presented by Osterkov and Anderson, Tapley and associates, Sachs, Burnet, Siegal and associates and Cannon and associates. From the viewpoint of phylogeny, Kahn's hypothesis seems highly probable.

Smith and Martin³⁴ pointed out that the phenomenon of bacterial allergy is entirely different from that of anaphylaxis. The reaction following the introduction of the antigen into an animal with the bacterial type of hypersensitivity does not appear until many hours after the injection is made. The hypersensitivity cannot be transferred passively to another animal by the injection of serum from a hypersensitive animal, and if tissue cultures are prepared from animals with the bacterial type of sensitivity, exposure to the antigen will result in death of the cells of the tissue culture. In anaphylaxis a characteristic response is displayed by each animal species and some species are exceedingly difficult to sensitize and shock. Bacterial hypersensitivity on the other hand can be produced in almost any animal and there are no outstanding differences in the reactions obtained in different species of animals. The bacterial type of hypersensitivity as a rule follows the introduction of the antigen into an area of inflammation, which under natural conditions means infection. Smith and Martin³⁴ feel that in spite of the failure to demonstrate antibodies in the serums of animals with bacterial sensitivity it is the consensus of most investigators in the field that bacterial hypersensitivity is a true antigen-antibody reaction. The antibodies, however, appear firmly attached to the tissue cells and do not occur in sufficient amounts in the circulation to be detectable by any method developed at the present time. That antibodies must appear in the blood at some time is, Smith and Martin³⁴ feel, suggested by the fact that the tissues all over the body become hypersensitive and a reaction will occur to the injection of the antigen at any site. They also pointed out that Chase has transferred sensitivity to tuberculin from sensitized to normal guinea pigs by the injection of leukocytes from pleural exudates.

The description of bacterial allergy presented by Smith and Martin³⁴ correlates very closely with the picture of granulomatous inflammation presented by Forbus.¹⁴ This suggests that there are real differences between the defense mechanism of granulomatous inflammation and that of suppurative inflammation although there is a fundamental, rather close relationship.

In discussing the modern concept of inflammation, Menkin²⁴ stated that inflammation is a manifestation of severe cellular injury in higher forms. As such, the inflammatory reaction requires the presence of vascular and lymphatic structures as well as tissue cells. The reaction, which is initiated by a disturbance in fluid exchange manifested primarily by an increase in capillary permeability, tends to be stereo-patterned. Close scrutiny reveals throughout a fundamental pattern which is largely referable to various basic common

denominators or biochemical units liberated by injured cells irrespective of the nature of the stimulating irritant. The initial increased capillary permeability and the early migration of polymorphonuclear cells are primarily caused by a polypeptide to which there may be attached a prosthetic group called leukotaxine. Leukotaxine has no similarity to histamine and has no relation to the H substance of Lewis. Leukotaxine fails to alter the number of circulating leukocytes when administered intravenously.

A leukocytosis promoting factor (L. P. F.) is liberated by injured cells and can in turn be recovered from exudates. The factor is thermolabile and nondiffusible. It can be extracted in the pseudoglobulin fraction of exudates, and cataphoretic studies suggest its association with α^1 and α^2 (α^1 and α^2) globulins of exudates. L. P. F. promotes a discharge into the circulation of immature granulocytes. It is present in human exudate but is absent from normal blood serum.

Menkin²⁴ found that there is also liberated by injured cells a toxic substance called "necrosin" which either is a euglobulin or is associated with the fraction in exudates. Its cutaneous injection is followed by swelling, redness, varying degrees of central necrosis, lymphatic blockade, injury to the endothelial walls of the blood vessels and swelling of collagenous bundles. Necrosin is absent from normal blood serum, but it may be recovered from the serum of an animal with inflammation.

The whole euglobulin fraction of exudates not only induces a conspicuous degree of cellular damage but also causes both a rise in temperature and a marked drop in the leukocyte count—a state of leukopenia. The fever producing factor can be separated from the true euglobulin by a method of differential solubility. This pyrogenic factor has been termed "pyrexin." It is thermostable. Its action is probably central, for pentobarbital sodium (nembutal) and antipyretics tend to reduce its effect. The leukopenic factor of exudate seems closely associated with pyrexin. The presence of such a factor in exudative material, particularly if the exudate is at an acid pH, may be of help in explaining the leukopenia attending numerous inflammatory processes. Pyrexin in exudates liberated by injured cells opposes the L. P. F. in its mode of action. The level of leukocytes in the circulation may be the resultant of these two opposing tendencies.

This work of Menkin²⁴ seems to supplement the hypothesis of tissue immunity presented by Kahn.¹⁵ These substances in the cell, released by injury, might be considered to be some of the nonspecific

natural antibodies to which Kahn¹⁵ referred. The liberation of necrosin, with the production of a lymphatic and capillary blockade, seems a better explanation for tissue necrosis than Kahn's admittedly halting suggestion¹⁵ of lymphatics and capillaries blocked by bacterial antigen in excess. This does suggest, however, that contrary to Kahn,¹⁵ necrosis is also a defense mechanism concerned with the localization of bacteria or bacterial antigen. Nothing in Menkin's work²⁴ denies the possibility of the development of antibodies by the cell, or the ability of cells under certain conditions to fix bacterial antigen and react to subsequent antigen circulating in the blood serum with cell damage and tissue necrosis.

Liberation of necrosin without the L. P. F. might explain why in lethal granulomatous ulceration of the nose and pharynx there is so often fever without the expected increase in leukocytes or change in the differential count.

This review suggests that altered reactivity in the defense mechanism can produce at least two types of allergy. The one, encountered especially in pollinosis and inhalant allergies, is associated with humoral antibodies; the other, encountered in idiopathic granuloma, is not necessarily associated with circulating antibody but is primarily associated with the development of hyperimmune areas in the body. These two types of reactivity are not mutually exclusive but may be combined.

The answers to the first and second questions proposed seem to give little difficulty. Granuloma formation is the body's method of resistance to certain preferred stimuli; the midline tissues of the face frequently are involved because in this region localized areas of immune cells tend to develop.

THE PATHOGENESIS OF IDIOPATHIC GRANULOMA

Teilum⁴⁰ has reviewed the literature on nonspecific granulomas and diseases related to them. He stated that by looking on these lesions from a common pathogenetic viewpoint based on morphologic observations and experimental studies on the vascular and tissue changes in allergy, by Gruber,⁴¹ Jäger⁴² and Rössle,⁴³ essential support has been obtained for the concept that these lesions are primarily vascular and are of allergic nature. It ought to be expected, therefore, that the physiologic mechanism would be similar in all cases, owing to a particular way of reacting to various agents of infectious toxic nature.

According to Klinge,⁴⁴ the essential morphologic substrate of these related conditions is a swelling of the ground substance (col-

lagen) of the connective tissue. This applies to the blood vessels which are involved in the process, with edema, fibrinoid degeneration and swelling of the collagen fibrils in all the layers of the walls of the vessels as the first morphologic change. The fibrinoid swelling (necrosis) of the ground substances is interpreted as an increase in the toxic damage that otherwise manifests itself as diffuse edematous swelling. Klinge⁴⁴ believed nonspecific granuloma to be an allergic lesion which pathogenetically is closely related to rheumatic fever as well as to allergic vascular lesions such as periarteritis nodosa and lupus erythematosus disseminatus. Therefore he felt that the necrotizing inflammatory processes in the connective tissues around the larynx and so forth are pathogenetically of quite the same character as the areas of necrosis in lungs and lymph nodes found in other vascular lesions of an allergic character and that they signify an allergic tissue reaction. Corresponding necrotic processes may occur in various organs.

It is of interest in this regard that Wegener⁴⁵ observed periarteritis nodosa to be a common finding in patients with lethal granulomatous ulceration. He felt that the condition causing the granuloma and that causing the periarteritis nodosa might be the same. He also pointed out that periarteritis nodosa was found in virus diseases and in rickettsial disorders and offered the suggestion that a viral invasion might be responsible for lethal granuloma. Gerlach⁴⁶ in addition described necrosis of arterioles at the site of the Arthus phenomenon (and the observation has been confirmed repeatedly). Periarteritis nodosa therefore would seem to be the same necrotic vascular reaction appearing in somewhat larger vessels that causes the Arthus phenomenon when it involved capillaries.

Weinberg,⁴⁷ in discussing periarteritis nodosa in granulomas of the type (idiopathic) considered in this paper, stated that the striking feature of the cases which have been studied thoroughly and fully reported is that they all present a history of long-standing upper respiratory infection with the development of ulcerations of the nose, mouth and trachea and with final development of the picture of periarteritis nodosa. He felt that the problem resolved itself into the explanation of the granulomas and their relationship to the periarteritis nodosa. Although iodism, glanders, tularemia, leprosy, rhinoscleroma, blastomycosis and sporotrichosis all give a somewhat similar histologic picture, Weinberg⁴⁷ could not demonstrate the etiologic agent in each of these diseases in the cases he studied and he could not obtain a history of related exposure. He considered the possibility that a virus might be the causative agent, but he stated that of the viruses only that of venereal lymphogran-

uloma produces a microscopic picture which is conceivably similar. He felt, therefore, that we are left with a picture which clinically consists of ulcerations of the upper respiratory tract associated with evidence of focal alterations in the lungs and anatomically shows multiple granulomas of unknown origin, involving one or more organs with terminal development of periarteritis nodosa. Weinberg⁴⁷ felt that the constancy of the history of antecedent chronic infection in these cases lends support to the belief that hypersensitivity may be a factor in their development.

In histologic study of material from four asthmatic patients who died, Harkavy⁴⁸ found that the chief pathologic changes responsible for the granulomas and periarteritis present were due to varying degrees of hyperergic and anergic vascular reactions in the tissues involved.

Rich and Follis⁴⁹ found that an Arthus phenomenon could not be produced in a tissue devoid of blood vessels. These investigators caused capillaries to grow into the cornea of one eye of sensitized rabbits. A small drop of the foreign serum to which the animal was sensitized was injected into the cornea at a short distance from the capillaries. A similar injection was made into the cornea of the opposite, nonvascularized eye and into the vascularized cornea of normal control animals. An Arthus type of reaction occurred in the vascularized cornea of the sensitized rabbits but not in the nonvascularized eye, nor in the vascularized eye of the control animals.

It would seem, therefore, that evidence is at hand which suggests that one of the fundamental resistance mechanisms of the animal is a typical localized cellular immune response, primarily vascular, resulting in "the Arthus phenomenon" when capillaries are involved, producing a granuloma in deeper tissues or a granulomatous ulceration if skin and subcutaneous tissues are involved. The granulomatous ulceration has a certain tendency to occur in the midline of the face, but is by no means confined to this location. There seems to be a certain tendency for the involvement of the larger vessels (periarteritis nodosa) to occur toward the end stages of the disease. The end stages of the disease also seem to be associated with marked lethargy and weakness on the part of the patient (addisonoid symptoms). The lesions produced by microorganisms are clinically and fundamentally identical with the idiopathic lesions. Therefore if "allergy" is the cause of the non-specific lesions, it would seem logical that such "allergy" is a dysfunction of the immune mechanism that normally produces granulomas.

Rich and Gregory⁵⁰ reported an experimental demonstration that purported to show that periarteritis nodosa is a manifestation of hypersensitivity. They stated that in their study periarteritis nodosa had been reproduced in all of its essential details in the experimental animal by creating conditions similar to those obtaining in serum sickness in the human being. They stated, "The demonstration that periarteritis nodosa is a manifestation of anaphylactic hypersensitivity is in line with the long recognized fact that the blood vessels are susceptible to anaphylactic injury." They pointed out that the anaphylactic wheal is in itself a result of capillary damage produced by increased sensitivity and the Arthus phenomenon is clear evidence of a more marked vascular injury. They reported that after a single large injection of serum their animals developed the capacity to react to the small intracutaneous test dose of 0.1 cc. of serum with large persisting lesions which in 5 of 14 animals were hemorrhagic and in 4 were necrotic or examples of the Arthus phenomenon. This is additional evidence that the same physiologic mechanism produces the lesions in both periarteritis nodosa and granulomatous ulcerations.

In discussing the pathology of sulfonamide allergy in man, More, McMillan and Duff⁵¹ stated that the fundamental pathologic change that is elicited by the allergic reaction is not apparent because there is no evidence that any single tissue is the primary reactant. Basically all the lesions are a complex of tissue destruction and of proliferation of the reticulo-endothelial cells in the affected area. They could not determine whether necrosis or reticulo-endothelial activity was the cause or effect of the reaction.

Boyd⁵² stated that he had encountered a case of disseminated lupus erythematosus with very characteristic collagenous degeneration in the glomerular tufts and also in the vessels of the lungs. In association with these changes in the lungs there were beautiful granulomas extremely like sarcoid lesions. These were situated in relation to arteries.

Duff⁵³ reported the study of 22 cases in which necropsy was performed and in which the patient had received sulfonamides during life. These cases showed either a granulomatous lesion (13 cases) or acute necrotizing arteritis (7 cases) or both lesions in common. Duff⁵³ felt that the granulomatous lesions and the necrotizing arteritis were closely comparable with periarteritis nodosa. He stated that whatever may be regarded as the etiology or pathogenesis of these lesions, the evidence gave strong support to the idea that the granulomatous reaction encountered in some cases

of periarteritis nodosa belongs to the same disease or rather is a part of that disease. He felt that his observations supported the view that all of these lesions are of "allergic" nature.

Weinberg⁵⁴ objected to the concept that the "allergy" present in such cases was to sulfonamides. He pointed out that cases showing the same granulomatous reaction with particular involvement of the lungs and upper part of the respiratory tract and associated with periarteritis nodosa have been reported in the literature as far back as 1906. Furthermore the patients on whom Wegener reported in 1939 did not receive any sulfonamide drug therapy.

From the evidence presented, which is very convincing, we should be able to consider granulomatous formation and periarteritis nodosa as essentially the same condition and apply evidence dealing with either, indifferently, to both.

Selye and Pentz⁵⁵ presented evidence that in man periarteritis nodosa can be the consequence of exposure to a variety of nonspecific damaging agents. Even in experiments on animals it was possible to reproduce the conditions by mere exposure to such nonspecific damage as cold. Periarteritis nodosa has been produced experimentally by Selye³¹ by overdosage with the adrenotropic hormone of the anterior lobe of the pituitary or hormones of the adrenal cortex. It has been claimed that the vascular changes produced by chronic overdosage with desoxycorticosterone are secondary to the hypopotassemia induced by this compound. Selye³¹ disagreed with this view, since the giving of excess potassium failed to protect against these lesions in animals receiving excessive amounts of desoxycorticosterone. It appeared more probable to him that the salt-active corticoids produce such changes by virtue of their sodium-retaining property. This interesting observation recalls to mind that many authors have suggested that a tendency toward allergy (hypersensitivity-hyperimmunity) is promoted by the sodium ion. Selye³¹ has found that in conditions of long-continued stress, such as are present in nonspecific granulomatous ulcerations of the midline tissues of the face, the hypophysis produces increased amounts of corticotrophic hormones. Selye suggested the possibility that through alterations in the corticotrophic hormones or in adrenal cortical responses any type of alarming stimulus may cause a condition of "relative adrenal cortical insufficiency," in which there is an increase in the production of the sodium-retaining corticosterones such as desoxycorticosterone at the expense of those corticoids which favor excretion of sodium ion and utilization of sugar, such as 17-hydroxy-11-dehydrocorticosterone. Selye³¹ has

also found evidence which makes it appear very likely that the initial acidosis of the shock phase of the alarm reaction is reversed during the countershock phase.

Petersen³⁰ has offered evidence that a relative alkalosis favors arteriolar and capillary constriction. Müller^{24, 25} Parrisius,²⁶ Brown²⁸ and others have found that a spastic state of the arterioles is associated with allergic conditions. Selye has also found evidence that the alarm reaction may have an important effect on serologic immune reactions. He has shown that the increased production of adrenal corticoids is followed by destruction of lymphocytes. Chase, White and Dougherty³⁵ and others have offered very convincing evidence that the lymphocyte is probably the principal source of gamma globulin, from which the antibodies appear to be formed. It would therefore seem probable that the humoral antibodies depend for their release on production of hormones of the adrenal cortex. It would not be surprising to find that these hormones played a part in the mechanism by which such antibodies are formed, and that "allergy" or hyperimmunity is concerned with changes in the activity of the adrenal hormones. A relative increase in the salt-retaining hormones and a relative decrease in the "antagonistic" hormones favoring secretion of sodium according to Selye appear to produce other conditions known to be associated with allergy. Beckman⁵⁶ and others have pointed out that increasing relative acidity of the body will tend to relieve allergic conditions. It would seem, therefore, according to Selye's³¹ hypothesis that in "allergy" we have a dysfunction of the alarm phase of the general adaptation mechanism rather than dysfunction of a specific mechanism having to do only with the adaptation of the body to the presence of micro-organisms. It is also obvious that the cell injury which releases the substance from the cells need not be by intervention of a toxin-antitoxin mechanism. Cell injury may be produced by the anoxia secondary to physical and emotional stimuli in unstable individuals. This type of cell injury can produce all the clinical features known as allergy.

To recapitulate, "lethal granulomatous ulceration of the nose, pharynx and larynx" appears by preference in that region because this is a region made up of large areas of skin and subcutaneous tissue in juxtaposition with mucous membrane and submucous tissue. Such tissues have an innate capacity to develop hyperimmunity, possibly greater than any other area of the body.¹⁵ Tissue immunity is from the phylogenetic standpoint the most primitive form of resistance to invasion by micro-organisms. The body tends to respond to invasion by micro-organisms which are meager pro-

ducers of toxin by a stereotyped reaction in which the earlier aggregation of leukocytes is replaced by plasma cells and macrophages as local immunity develops. This is accompanied by a "capillary and lymphatic blockade" with the formation of central necrosis caused by cutting off the blood supply. This is essentially the Arthus phenomenon. Associated with the production of central necrosis is the production of areas of panarteritis in some of the smaller and larger arterioles. This is essentially periarteritis nodosa. It is presumed that the same mechanism working in different sized vessels produces both phenomena. It has been shown that both the Arthus phenomenon and periarteritis nodosa can be produced in experimental animals by injection of nontoxic protein (anaphylactogen). It has been stated that idiopathic granulomatous ulceration and periarteritis nodosa together with rheumatism, Libman-Sachs syndrome, lupus erythematosus and other related conditions are instances of vascular bacterial "allergy."

Kahn,¹⁵ however, has suggested that the reacting areas are areas of tissue hyperimmunity where antibodies formed from insoluble globulins are in excess. At a subsequent infection these areas will extract antigens, specific or nonspecific, circulating in the blood and localize them in the area with production of the necrotizing and granulomatous vascular phenomena. Kahn suggested that allergic individuals are those who develop tissue immunity to substances to which normal individuals do not become immunized, develop higher degrees of immunity and develop it more readily than normal individuals. Kahn does not feel that the concept that all resistance to invasion of the body by micro-organisms has been taken over by certain specialized cells of the reticulo-endothelial system is tenable. Kahn's hypothesis explains the development of the Arthus phenomenon when the body is invaded by micro-organisms which produce little if any toxin and also how this phenomenon might appear in the absence of specific infection in a hyperimmune individual by activation of highly immunized areas of tissue by nonspecific, nontoxic proteins gaining entrance to the blood stream. Menkin²⁴ has found that damaged tissue cells release a substance associated with gamma globulin, necrosin, which is capable of producing the central necrosis which Kahn did not adequately explain.

Selye,³¹ however, presented evidence to indicate that periarteritis nodosa could also be produced by exposing an animal to such damaging stimuli as cold, fatigue or emotional perturbation. This effect was produced by stimulation of the adrenotropic hormone of the anterior pituitary which in turn stimulated the production of

hormones of the adrenal cortex. He found evidence which suggested to him that such stimulation caused a relative adrenal cortical insufficiency with excessive production of the salt-active hormones such as desoxycorticosterone and decrease in the "antagonistic" hormones such as 17-hydroxy-11-dehydrocorticosterone, as well as a decrease in the pituitary growth hormone, prolactin and gonadotropic hormones. During the period of excessive secretion even during the stage of exhaustion, the adrenal cortex is enlarged. Associated with these adrenal changes are changes in fluid and electrolyte metabolism (which are controlled by hormones of the adrenal cortex) with a rise in the pH, a retention of sodium ion in extracellular fluid, a tendency toward vasoconstriction with the production of localized tissue anoxia, conditions which have been long associated with "allergy." It therefore seems reasonable to assume that tissue immunity is a phase of the general adaptation mechanism, and that hyperimmunity or bacterial allergy occurs in individuals who have a tendency toward relative adrenal cortical dysfunction. "Allergy" in this case would have to be defined in the very broadest terms and the tendency to limit it to disorders of humoral immunity would have to be completely ignored.

Under this hypothesis an individual with lethal nonspecific granulomatous ulceration of the nose, pharynx and larynx would be considered one who suffered from a relative pituitary or adrenal cortical dysfunction.

Selye³¹ has indicated that periarteritis nodosa tends to develop more readily in the presence of high-sodium content of the body fluids but that even with such high-sodium content, acidifying salts such as ammonium chloride will tend to prevent the development of periarteritis nodosa.

Selye³¹ has suggested that in animals under prolonged overdosage of desoxycorticosterone a great tendency toward fatal hypoglycemia develops. Under the influence of prolonged alarming stimulation, such as would be provided by a lethal granuloma according to Selye's hypothesis, the same condition should be expected. In lethal granuloma the extreme weakness and lethargy of these patients are noteworthy and several authors have referred to their "addisonoid" symptoms.

Since Selye³¹ has suggested that under certain conditions of strain the adrenal cortex may produce disproportionate and excessive amounts of salt-active corticoids with a relative deficiency of sugar-active corticoids, these effects could probably best be counteracted by the giving of adequate doses of such a substance as 17-hydroxy-

11-dehydrocorticosterone, which is known to counteract some of the malign effects of overdosage of desoxycorticosterone. Selye stated that if resistance were dependent to any great extent upon increased corticoid hormone production, treatment with corticoids should have given more satisfactory results than have so far been obtained. In this connection he pointed out, however, that it is of interest to note that even the basic corticoid hormone production of the adrenal is apparently enormous in comparison with the amount of corticoid substance that has been administered for therapeutic purposes. Thus bio-assays performed on the venous blood of adrenal glands indicate that "the average output of one suprarenal gland per minute per kgm. body weight was equivalent to 0.6 gm. of suprarenal tissue." "The potency of 1 ml. suprarenal plasma was at least several times, occasionally 10-12 times, as high as the activity obtained by extracting 1 gram of gland."

There is very convincing evidence, Selye³¹ felt, that in combating damage during the alarm reaction the sugar-active corticoids are effective, but there is doubt whether the salt-active corticoids which are readily available commercially are of any value. Since commercial preparations of sugar-active corticoids are often impure and not available, it is not surprising that up to the present it has rarely been possible to improve markedly upon the natural performance of the adrenal cortex. It would seem, therefore, that to test the curative effect of this hypothesis in lethal granuloma we must wait for better or greater production of the necessary hormones.

The unanswered questions are answered in the review of the literature.

First, the occurrence of granulomatous inflammation without an adequate normal stimulus can be considered a type of allergy. Second, this dysfunction appears to rest on a disorder of the secretion of 17-hydroxy-11-dehydrocorticosterone (compound "E" of Kendall) and the disorder is fundamental in producing all the dysfunctions, such as relative alkalosis, relative anoxia, capillary permeability and so forth, that are considered to be characteristic of the allergic state.

REPORT OF CASES

CASE 1.—A woman, 48 years of age, gave the history that about three and one-half years previous to her visit to the clinic ulcerations of the mouth which were cyclic in character had begun to develop. They would appear every six months and last for three months; the patient had felt very well in the intervals. She lost weight and strength with each attack but recovered between times. On several occasions she had received penicillin for a few days with apparent benefit. About a year after the ulcers in the mouth first appeared, a yellow-green puru-

lent discharge from both sides of the nose developed. The patient stated that some type of intranasal operation had been done in January of that year without any evident influence on the symptoms. During the following year she had received penicillin and sulfonamides at irregular intervals and felt relatively well during this entire time. In February of the ensuing year, however, there had been a marked increase in the nasal discharge and recurrence of the sores in the mouth which extended posteriorly, producing considerable pain on swallowing. Treatment at home no longer helped. She had been hospitalized and received penicillin for eight days and a sulfonamide for three days without any particular effect on the lesions. In June of that year hoarseness had developed and the left eye had become red and inflamed. About the same time red, swollen and painful gums developed and two weeks later a red crusted lesion about the size of a five-cent piece appeared on the right shin and a little later several others on the same leg, and a subcutaneous nodule was found on the left thigh. A month later an ulcerated lesion about the size of a nickel developed on the dorsum of the right forearm and a subcutaneous nodule on the flexor surface of the left forearm. There was no bullous formation preceding the appearance of these lesions and there had never been a purulent character to the discharge from them. From the first there had been nothing but the development of a dry leathery crust with no pain or secretion. The general symptoms of anorexia, fatigue, loss of weight and a feeling of fever developed.

On examination in the Section on Otolaryngology and Rhinology the nasal septum was found thickened on the left by a granulomatous-appearing ulceration which was covered by a tenacious yellowish exudate. Attempts to remove the exudate resulted in bleeding. The nasal mucosa was pale and swollen and had a peculiar granular appearance. On examination of the mouth the gingivae were found to be swollen and congested. There was a superficial ulceration on the left side of the tip of the tongue and there was a ragged, shallow ulceration involving the soft palate, the uvula and the posterior pharyngeal wall. The base of the ulcerated area was covered with a tenacious, yellowish gray exudate. The entire larynx had an edematous appearance, especially marked in the epiglottic folds. The vocal cords, while a little thickened, appeared relatively normal.

Of three consultants in the Section on Otolaryngology and Rhinology who examined the patient on admission, one felt the lesion represented Boeck's sarcoid, one thought it might be either Boeck's sarcoid or tuberculoma but felt that serologic tests for syphilis should be checked carefully and the third felt that the lesion was unquestionably tuberculosis.

Examination of the eyes was reported to show a possible scleritis of the left eye. Fields were roughly negative. Fundus examination showed the retinal arterioles to be slightly narrowed with a few hyaline spots in the choroid on the right.

General physical examination showed a slightly emaciated woman having a five-cent-sized discrete, crusted, depressed erythematous lesion on the dorsum of the right forearm. There was a similar erythematous macule on the right shin and a smaller lesion near the right knee. There were several pea-sized crusted macules on the left thigh. There was a slightly tender, firm, subcutaneous nodule posterior to the left ankle and a tender, erythematous nodule under the skin of the flexor surface of the left forearm.

The dermatologic consultant who saw these lesions felt that the differential diagnosis lay between an "id" reaction from the granulomatous lesions in the mouth and pharynx, a deep mycosis such as coccidioidomycosis, histoplasmosis or moniliasis, papulonecrotic tuberculid, atypical pemphigus or erythema nodosum with the possibility of lymphoblastoma to be considered also.

A specimen for biopsy was taken from the lesion on the left side of the nasal septum and was reported to be "inflammatory tissue." A second speci-

men was immediately taken and reported to be "very inflammatory tissue." Nothing suggestive of tuberculosis, fungous infection, protozoan infection or a malignant lesion was seen. The results of examination of the sputum were negative for acid-fast bacilli and [a roentgenogram of the thorax was reported to be negative except for the presence of bilateral calcified hilar nodes.] The patient was seen by a consultant from the Section on Bacteriology who took scrapings of the tissue for culture and smear and a specimen for biopsy from the lesions of the nose, palate and pharynx. Several smears were negative for acid-fast bacilli. Cultures were found positive for *Staphylococcus aureus* and *Neisseria catarrhalis*. The specimens for biopsy from the nose and throat were positive for *Staphylococcus aureus* (great numbers). A peculiar feature reported was the diffusion of the staphylococci through the tissues without any apparent effort on the part of the body to limit their advance. The growth of these staphylococci was completely inhibited by 0.1 unit of penicillin per ml. and by 6 micrograms of streptomycin per ml.

Study of the blood revealed 4,040,000 erythrocytes and between 3,000 and 5,000 leukocytes per cmm. The concentration of hemoglobin was reported to be 12.7 gm. per 100 cc. Differential count showed 25% lymphocytes, 3% monocytes, 70% basophils. A smear of the blood was reported to show toxic polymorphonuclear leukocytosis with a fairly well marked left shift. There was some hypochromasia. Nothing diagnostic was seen. Bleeding time was reported to be 5 minutes and coagulation time 4 minutes and 30 seconds. Prothrombin time was reported to be 23 seconds. Sedimentation rate by the Westergren method was found to be 43 mm. per hour. The results of Kline, Kahn, Hinton and Wassermann tests were reported negative. A roentgenogram of the sinuses was reported to reveal thickened membrane in all the sinuses.

It was therefore decided on the basis of these findings that we were dealing with a nonspecific granuloma of the type seen in gangosa but that the staphylococci might be playing a part.

A consultant in antibiotic therapy saw the patient, reviewed the findings and advised giving 1,000,000 units of penicillin daily by continuous intravenous drip for a minimum of three weeks. The patient was hospitalized and the therapy was started. The third day the patient's temperature rose to a peak of 102° F. and after this she had a daily remittent fever with peaks of between 103° and 105° F. throughout the remainder of her course in the hospital. Daily leukocyte counts showed from 5,000 to 8,000 cells per cmm. with a normal differential count on smear. In fact the number or percentage of the different white blood cells did not vary throughout the patient's illness and showed little evidence that the patient was suffering from a serious disease.

At the end of three weeks of penicillin therapy little change could be seen in the appearance of the lesion or in the patient's condition. The consultant in clinical bacteriology again saw the patient and again took smears and specimens for biopsy from the pharynx and larynx. At this time cultures were found negative for staphylococci but there were many colonies of *Candida* (*Monilia*) *albicans* present. The biopsy showed these organisms to be infiltrating between the tissue cells in the same uninhibited manner that the staphylococci had been seen to do in the previous biopsy, performed before penicillin was given.

It was then decided to try the effect of transfusions. Eleven transfusions of 500 cc. of whole blood were given at intervals of ten days. At the same time vitamin K, liver extract with copper and iron, and capsules containing several times the known minimal daily dose of the several vitamins were given daily. For a week folic acid was also given daily. These treatments did not affect the patient's local condition and during this time several subcutaneous nodules and dry necrotic ulcerations of the skin on the legs and arms developed. Blood cul-

tures were repeatedly negative. A swelling of the right leg to the groin with tender red lumps under the skin developed.

A consultant in vascular disease who was called in felt that there might be a thrombosis of the right femoral vein, but the red, round tender areas, chiefly in the upper mesial region of the thigh, felt more like erythema nodosum than phlebitis. He felt that he could not differentiate satisfactorily between deep venous thrombosis and a superficial lesion with edema. He suggested the possibility that periarteritis nodosa might be present and asked that a biopsy of one of the tender nodules be done.

Another consultant in internal medicine, who was called in, expressed the opinion that the patient had infection with *histoplasma capsulatum*. He felt that this hypothesis would account for all the symptoms and signs, especially the lack of response to penicillin. He felt that the cutaneous and mucosal lesions, the fever and the systemic manifestations all fitted very well. He pointed out that biopsies of skin and mucous membrane and even the results of cutaneous tests may be negative, and the exact diagnosis may be impossible to make except post-mortem.

The dermatologic consultant agreed that histoplasmosis was a most probable diagnosis, but protested that in spite of repeated search for organisms on repeated specimens he had been unable to find the organism. The patient consented to another biopsy and a portion of tissue was sent to the consultant on clinical bacteriology, another to the consultant on clinical mycology and a third to the dermatologic pathologist. Cutaneous tests for histoplasmin and coccidioidin were repeated and the results were negative. Tissue from the pharynx and forearm was reported negative for acid-fast bacilli and fungi by the mycologist, the bacteriologist reported smears and cultures negative except for a few colonies of *Candida albicans* and the pathologist reported tissue from the pharynx to be a "granuloma," the tissue from the right forearm to show a nonspecific subacute granuloma with necrosis and the lesion from the left arm to be lupus erythematosus. Evidence of periarteritis nodosa could not be found.

In view of the possibility of the disorder being histoplasmosis, 6 gm. of sulfadiazine daily in divided doses was given for 21 days. Since this appeared to have no effect on the progress of the disease, 2 gm. of streptomycin daily was given for 17 days, also without apparent effect.

A consultant in hematology was then asked to see the patient. He felt that the hypertrophy of the upper gums with increase in the interdental tissues resembled that commonly seen in monocytic leukemia. He did two sternal aspirations. He found numerous units variable in size, all floating in the fixing solution. Nothing abnormal was found. He made the comment, "This is pretty good looking bone marrow, and I can find nothing helpful." He suggested, however, that the patient be treated with roentgen therapy as though the case were one of monocytic leukemia. This was done. After the roentgen therapy the patient reported subjective improvement but there was no observable improvement in the lesions present.

The temperature began to rise to peaks of 104° and 105° F. daily. Blood and urine cultures taken at the peaks of fever were repeatedly negative. The results of inoculations of guinea pigs done when the patient was first admitted were reported negative. The dry, necrotic cutaneous lesions began to increase in number, pleuritic pains in the thorax developed, the lesions in the palate and pharynx became more necrotic and the soft palate split in half.

The consultant in clinical pathology saw the patient again and took numerous cultures and smears. All cultures showed a pure, heavy growth of *Staphylococcus aureus*. No anaerobes were found. He stated that the staphylococci found were resistant to penicillin, requiring 15 units per cc. to cause inhibition of growth. They were also quite resistant to streptomycin, requiring 6 to 12 units per cc. to

inhibit growth. Whatever the primary cause of her illness, this patient, he felt, was "now riddled with a virulent *Staphylococcus aureus*, which is so resistant to the antibiotics that their use would be of questionable value."

Although up to this time the patient had appeared surprisingly well, she suddenly became very weak and exhausted, displaying marked Addisonoid symptoms. She became dehydrated and she was unable to swallow food because of the pain of the pharyngeal lesions; it was no longer possible to find open veins for intravenous administration of fluid. Tube feedings were started, 2,000 cc. of a high caloric mixture made up to 3,000 cc. with water being given daily. Dr. Kendall kindly supplied us with a quantity of his extract of the adrenal cortex, 100 cc. being given intramuscularly. The patient seemed to show a sudden marked improvement after this injection but the next day her temperature rose to 106° F. and remained there and she died in the afternoon, apparently of exhaustion.

The Section on Pathologic Anatomy made detailed examinations of the tissues of this patient. Five months later they reported that the case was still a puzzle to them. They found numerous abscesses of the skin and mucous membranes from which they could culture only *Staphylococcus aureus*. The internal organs showed absolutely nothing in the way of any specific change either as a basis for the involvement of the skin and mucous membranes or as a secondary manifestation of it.

The most striking things about this patient's illness appeared to be a rather startling appearance of well-being in the face of a serious disease, the lack of any marked response of the hemopoietic system to the infection, the lack of the usual leukocytic barrier to the invasion of tissues by micro-organisms and the daily high fever with apparent lack of the usual co-ordination between the febrile and leukocytic reaction to infection.

The absence of subjective illness, as well as the lack of response of the specialized defense tissue, both apparently indicate a disorder of function of the normal defense mechanism of the body.

CASE 2.—This patient, a man aged 45 years, was referred to the Mayo Clinic because of nasal and orbital symptoms. The referring physician stated that the patient, who had reported nasal sinusitis for "years" had first come to him two and one-half years previously because of swollen lymph nodes in the neck and axillae, following a series of slight colds. Examination then revealed palpable lymph nodes in the cervical, axillary and inguinal regions and a palpable spleen. A roentgenogram of the thorax was reported to reveal normal cardiac and lung field shadows. The mediastinal lymph nodes were not enlarged and there were no findings to suggest a mediastinal lymphadenopathy.

Examination of the blood taken at that time had showed 80% hemoglobin, 4,850,000 erythrocytes and 68,600 leukocytes per cmm., of which 90% were lymphocytes, 9% neutrophils and 1% eosinophils. The results of a complement fixation test for syphilis were negative. In the next two years repeated blood counts were taken. The patient was said to have received "some" roentgen treatment. In spite of this there was little change in the blood picture or roentgenographic findings. A diagnosis of "pseudoleukemia" appears to have been made. A year and four months before coming to the Mayo Clinic the patient had noticed swelling around both eyes and a profuse yellow purulent discharge from both sides of the nose, but he had not experienced any pain. Since its first appearance the swelling around the eyes had appeared and disappeared, affecting sometimes one eye and sometimes the other. The patient reported that just before he came

to the clinic a roentgenogram of the head was reported to reveal destruction of the ethmoid plate with extension of infection from the ethmoidal cells into both orbits. The physician who referred the patient to the clinic made a diagnosis of "granulomatous rhinitis and sinusitis, with progressive osteomyelitis of the bones of the face."

On examination at the clinic the patient did not appear to be acutely ill. Examination of the nose showed both nasal chambers filled with thick crusts and on removal of these crusts the mucosa was seen to be covered with a thick, tenacious, yellow, purulent exudate. The mucosa had a "peculiar" appearance, markedly thickened and "hyperplastic." On examination of the eyes the right lid was found to be reddened and greatly swollen. There was a fistula draining pus on the medial aspect of the right upper lid. There was a slight chemosis of the conjunctiva on the right and a slight proptosis but no limitation of motion. It was noted that blowing of the nose forced air through a fistula on the medial aspect of the left upper lid but not through the similar fistula on the right.

General physical examination revealed little except a "good number" of palpable lymph nodes in both axillae and a few in both inguinal regions. The spleen was palpable but the liver was not palpable. Examination of the blood showed a concentration of hemoglobin of 11.9 gm. per 100 cc. with an erythrocyte count of 4,840,000 per cmm. There were 18,600 leukocytes present per cmm. Differential count showed 17.7% lymphocytes, 6% monocytes, 76% neutrophils and 1% eosinophils. After examining blood smears the hematologist reported that a leukocytosis with lymphocytosis was present. There were no immature forms seen and it was felt that the blood picture resembled that characteristic of a toxic process. A sternal puncture was done and the hematologist reported that although a leukocytosis with about 60% lymphocytes was present, he was unable to find any immature cells to substantiate a diagnosis of chronic lymphatic leukemia. Another sternal aspiration was done in the usual manner and a satisfactory specimen was obtained. There were many units and they varied greatly in size. Examination of the unconcentrated and concentrated smears showed an unusually large number of mature lymphocytes with bluish cytoplasm and a rather heavy blocked chromatin nucleus. Other bone marrow elements did not seem to be particularly disturbed and on the unit touch preparations it was seen that these lymphocytes occurred in masses and spread out in chains. There were essentially no mitotic figures present and the lymphocytes looked mature. The fixed preparation was very good and showed the bone marrow to be largely replaced by lymph follicles. Again there were no mitotic figures present and the lymphocytes looked mature. The hematologist stated that "this should be a chronic lymphatic leukemia although we would be unable to differentiate it from a lymphosarcoma."

Roentgenograms of the sinuses revealed cloudiness throughout. The result of a flocculation test for syphilis was reported to be negative. Cultures from the nose were reported to reveal a streptococcus (hemolytic) and a micrococcus. A culture from the orbital abscess planted on hormone blood agar (P&S) and dextrose agar did reveal fungi, but a culture on ordinary mediums showed many colonies of hemolytic streptococci. A culture taken from the right sphenoid was reported to reveal *Staphylococcus aureus* with a sensitivity to penicillin between 100 units and 10 units per cc. On another culture from the nose many colonies of gram-negative rods which were felt to be *Pseudomonas* were found. Sputa examined were negative for sulfur bodies and acid-fast bacilli. The sedimentation rate by the Westergren method was 28 mm. per hour. On the basis of these examinations it was felt that the condition present was "compatible with a diagnosis of lymphosarcoma or leukemia." Roentgen therapy was advised and was given over the orbits, sinuses and splenic region. The patient was dismissed and told to return in a month. After dismissal he was able to return to his work as a bank clerk, but a week before his return he caught a slight cold with marked increase in

the swelling and induration about the eyes. Except for this increased swelling, the patient's condition was about the same as on dismissal. Further roentgen therapy was given with an apparent marked improvement in the condition of the induration about the eyes. During the patient's stay in the hospital on these two occasions he received 160,000 Oxford units of penicillin every 24 hours.

This patient returned again in two months because dermatitis of his upper lip and right ear had developed. All penicillin therapy was stopped and the dermatitis cleared up in a month under wet dressings with 1:16,000 potassium permanganate solution. During the interval that the patient had dermatitis his nose and eye condition seemed to improve markedly.

He returned again in about two months with a marked flare-up in his nasal and orbital symptoms following a slight "cold." At this time his blood count showed 6,700 leukocytes per cmm. and a blood smear was reported to show mild lymphocytosis with some cells a little immature. The general medical consultant felt that there was insufficient adenopathy or blood changes to warrant further roentgen therapy.

At this time the ophthalmologist expressed the opinion that the sinus infection was maintaining the disease in the eyes and since the medical men were now inclined to doubt the diagnosis of leukemia, it was decided to try the effect of surgical treatment of the sinuses.

Bilateral naso-antral windows were made and both sides were found to contain a large quantity of foul pus with a tremendously thickened and degenerated mucosa which was curetted out. The middle turbinates on both sides were inflected toward the midline and the ethmoidal labyrinths were entered through the bulla ethmoidalis on both sides. The anterior and posterior ethmoidal cells on both sides were very seriously diseased and on opening into the sphenoidal sinuses both were found to be similarly involved. Very large openings were made from the nose into both frontal sinuses. Both were found filled with foul pus and diseased membrane. After removal of the diseased tissue on the right side an area of dura measuring about 2-3 cm. and covered with infected granulation tissue was revealed. The dura in this area could be seen to pulsate. The middle turbinates on both sides were preserved in their entirety.

After the operation the patient seemed to make a spectacular recovery. The orbital lesions cleared up, the nasal discharge stopped and he seemed to have regained excellent health. Five months later, however, he contracted a "cold in the head." Two weeks later he was brought into the hospital in an apparently serious condition. Perforations had developed above the inner canthus of both eyes, there was a return of the purulent nasal discharge, the patient had lost much weight and he was severely short of breath.

The consultant in general medicine felt that the condition resembled a chronic infection rather than a leukemia. Blood counts taken at the time showed 22,000 leukocytes per cmm. with 21% lymphocytes and 76% neutrophils. Blood smears were reported to show leukocytosis with toxic polymorphonuclear leukocytes. There were some very abnormal, rather immature lymphocytes. It was felt that the blood smear was not diagnostic. The hematologist expressed the opinion that the condition was definitely not chronic lymphatic leukemia but probably represented some kind of lymphoma which might be on an infectious basis. A roentgenogram of the thorax showed fluid in the left pleural space with displacement of the heart toward the right. The thoracic consultant felt that if he had nothing but the roentgenogram of the thorax and findings to go on he would strongly favor a diagnosis of tuberculosis, but he was not sure if this would fit in with other features of the situation. Thoracentesis was done and 600 cc. of clear dark brown fluid was removed without difficulty. The fluid was found to have a specific gravity of 1.018 and contained 1,900 cells per cmm.; there were

285 mg. of fat per 100 cc. and 3.3 gm. of protein. The pleural fluid was found negative for bacteria and negative for acid-fast bacilli.

The patient was given 1,000,000 Oxford units of penicillin per 24 hours and appeared to be making favorable progress when at 1:30 p.m. of the sixth day after admission he suddenly became orthopneic and cyanotic and appeared to be in a critical condition. It was felt that a pneumothorax had developed on the left. Three chest taps were done, withdrawing more than 2,000 cc. of air and about 200 cc. of cloudy yellow fluid. This did not improve the patient's condition and he died during the night.

Pathologic examination of the body of the patient failed to resolve the dilemma as to the type of condition. After exhaustive examination of microscopic sections the pathologists reported this case to represent a "lymphoma." They could not classify it further.

The striking feature of this case seemed to be the patient's lack of resistance to mild infections of the upper part of the respiratory tract. Each infection would cause a tremendous inflammatory reaction in the midline tissues of the face, suggesting bacterial hyperimmunity in the area with an "Arthus" type of reaction to indifferent intercurrent infections. During the entire course of the illness the patient's temperature never rose to more than 100° F. He reacted to mild stress very much like an adrenalectomized animal.

CASE 3.—A man, aged 21 years, was admitted to the hospital for emergency treatment. Since he was from Mexico, his examination had to be conducted through an interpreter. He stated that seven months before his admission congestion of the right side of the nose had developed. Two weeks later a "canalization" into the right maxillary sinus had been done. Pain and tenderness of the right malar region had developed almost immediately with hyperesthesia of the upper teeth on the right. A thick sanguinopurulent exudate began to run from the right side of his nose almost immediately and continued without interruption until his admission. He began to have a fever. A month before his admission the process extended to his right ear and subsequently the ear discharged continuously. A short time before his admission inflammation and induration extended into the upper part of the right side of the neck.

Examination was done with some difficulty because of a very low pain threshold. On examination of the ears, nose and throat, after shrinkage, both nasal chambers were found filled with a granulomatous mass which bled easily. Specimens were taken, biopsy of which was reported to show very inflammatory tissue with numerous polymorphonuclear neutrophils and lymphocytes, also eosinophils and plasma cells. The right upper gingiva was swollen and tender. The right ear was filled with a thick sanguinopurulent exudate which on removal revealed a perforation in the postero-inferior quadrant of the eardrum.

The result of ophthalmologic examination, including examination of the fundi, was negative.

On general physical examination the patient was reported to appear obviously ill with pains "everywhere" in the hands, feet, abdomen, thorax and neck. Nothing was found on examination except some enlarged nodes in the axillae and groins. The patient's temperature was 102° F. Roentgenograms of the mastoids were reported to be negative, but those of the sinuses were reported to show thickened membrane in the right antrum, both ethmoid cells and frontal sinuses. A roentgenogram of the thorax was reported to be negative.

Examination of the urine revealed the presence of erythrocytes, grade 2 to 3 (on the basis of 1 to 4, in which 1 indicates the least and 4 the greatest devia-

tion from the normal). Examination of the blood showed 14.8 mg. of hemoglobin per 100 cc. of blood. There were 17,000 leukocytes per cmm. and differential count showed 18% lymphocytes, 4% monocytes, 76% neutrophils and 2% eosinophils. A blood smear showed toxic polymorphonuclear leukocytes containing Döhle bodies. There were considerable left shift, mild hypochromasia and increased regeneration. The results of repeated examinations of sputum were reported to be negative for *Mycobacterium tuberculosis*. A thick blood smear was negative for plasmodia. Agglutination reactions were negative for *Brucella*, typhoid and paratyphoid organisms. The result of a coccidioidin skin test, first strength, was reported to be positive, 2+. Repetition of this test with the second strength gave the same result. Cultures of the sputum on dextrose agar and hormone blood agar were negative for fungi. Cultures of pus from the ears and nose done on brain broth blood agar were reported to reveal the presence of hemolytic streptococci. Blood cultures were negative.

Owing to the fact that the patient's illness might be due to general invasion from the antrum, it was advised that the nose and antrum should be explored.

At operation the nasal chambers were found to be completely filled with granulation tissue. This appeared to have originated from the septum, which had been completely destroyed by the disease. The right antrum was found to be normal but both ethmoidal labyrinths contained granulation tissue and pus. Histologic examination of the tissue removed at operation showed a very inflammatory tissue with numerous polymorphonuclear neutrophils and lymphocytes, also eosinophils and plasma cells. Tissue cultures from the material secured from the nose and sinuses were positive for hemolytic streptococci but were negative for other bacteria or fungi.

The patient's condition failed to improve after the operation. One gram of emetine hydrochloride and 300,000 units of penicillin were administered every 24 hours and he was given a high-vitamin, high-caloric diet.

On the third day following operation the patient began to cough and complained of a pain in the thorax. A roentgenogram of the thorax showed pneumonia at the right cardiopleural angle, and on repetition a week later the roentgenogram showed some pulmonary congestion in both lower lobes. The patient began to complain of increasingly severe epigastric pain. A liver function test revealed dye retention, grade 3. The direct van den Bergh test for bilirubin revealed 1.2 mg. per 100 cc. of serum and the indirect test, 0.5 mg. per 100 cc. Owing to continuing hematuria an excretory urogram was done and was found to be negative. The source of the hematuria could not be determined by the urologist in the absence of cystoscopy, which was felt to be contra-indicated.

Sternal puncture and aspiration were done. Some small units were reported to be present, some floating and some sinking in the fixing solution. Examination of all the preparations showed a moderate cellularity, primarily of the neutrophilic line with a left shift. A majority of the cells, particularly on the touch preparations, were in the premyelocytic stage. On the concentrated smear a large number of mature polymorphonuclear leukocytes were present, and at the fringe there were a number of both phagocytic reticulo-endothelial cells and monocytoid reticulo-endothelial cells. The phagocytic cells contained pigment debris and occasionally some dark-staining material which it was felt might be nuclear debris. No organisms suggesting fungi or bacteria could be found in any of these cells. It was felt that the bone marrow was "not diagnostic" although of the type usually seen in an infectious process. The patient continued to have a high temperature, to have erythrocytes in the urine and appeared very toxic. There suddenly developed an eruption of a purpuric and vesicular type on the soft palate, also tending to occur in patches chiefly over the sternum, buttocks and lower back, elbows and forearms. On the soft palate were small (1-2 mm.) inflamed yellowish ulcers with red areolae. They were diffusely scattered over the entire surface of the

soft palate. The lesions on the skin were elevated, infiltrated skin-colored plaques associated with some firm acuminate papules. There were also a few hemorrhagic blebs and firm pustules with umbilicated centers. Examination of the blood at this time showed 6.0 gm. of hemoglobin per 100 cc. of blood and 2,450,000 erythrocytes and 10,800 leukocytes per cmm. of blood. Differential count showed 25% lymphocytes and 74% polymorphonuclear leukocytes.

The dermatologic consultant felt that these cutaneous lesions might be anaphylactic. Blood transfusions were started. A gallop rhythm with definite electrocardiographic changes suddenly developed. The following comment was then made by the consultant in internal medicine, "The patient has added another to the number of systems involved. The multiplicity and particularly the organs involved fit in well with the diagnosis of periarteritis nodosa. The low percentage of neutrophils in the differential count and the lack of response to penicillin are against an abscess of cryptic nature unless it is a granuloma." Biopsies were made of an axillary lymph node, a portion of the pectoralis major muscle, a small artery and a small vein. The pathologic report was: "Inflammatory lymph node. Normal muscle and artery. The vein shows slight perivascular infiltration about capillaries in its wall." Cultures of the tissues removed were negative for bacteria and fungi. Pulmonary edema developed and the patient died.

Necropsy revealed extensive granulomatous lesions in the trachea and bronchi. Small, yellowish nodules were found scattered throughout both lungs, especially in the lower lobes. Microscopic examination disclosed a large number of necrotizing lesions of the pulmonary arterioles and parenchyma as well as extensive granulomatous inflammation of the bronchi. Lesions of periarteritis nodosa were also found in the kidneys, liver and spleen.

The onset of the disease in this patient was more sudden and the course was less prolonged than in the others. The patient showed more evidence of illness with the disorder than the usual patient with lethal granuloma. This illness seems to be the reflection of active resistance. The leukocyte count, however, never rose to more than 17,000 per cmm. of blood and the percentage relationship between lymphocytes and polymorphonuclear leukocytes was never disturbed. It might seem that when there is a partial leukocytic response the larger vessels appear to be more involved with periarteritis nodosa, and when the leukocytic response is less marked the capillaries are involved in an "Arthus" lesion.

SUMMARY

Data on three cases of lethal granulomatous ulceration of the midline tissues of the face are presented. It is suggested that granuloma is the stereotyped defense mechanism by which the body resists invasion by micro-organisms which are feeble toxin producers. This same defense mechanism is utilized by the body when nontoxic protein material is injected.

Tissue immunity as outlined recently by Kahn¹⁵ is the immune mechanism involved. Dysfunction of this immune mechanism may occur as the result of hyperimmunity in certain areas with the development of the Arthus phenomenon or periarteritis nodosa or both.

Evidence suggests that both these lesions are produced by the same physiologic mechanism, affecting in one instance the capillaries, in the other the smaller arteries and arterioles.

According to Selye³¹ periarteritis nodosa may be produced by excess of the "salt-active" corticoids of the adrenal glands. He suggested the hypothesis of relative adrenal cortical dysfunction with excess production of the "salt-active" and relative suppression of the "sugar-active" corticoids. He has found that excess sodium ion and an increased pH favor the development of periarteritis nodosa under experimental conditions whereas elimination of sodium ion together with the giving of acidifying drugs will tend to prevent its development. Whether the interpretation of the experimental results obtained by Selye can be applied in clinical medicine must await further investigation. The availability of the hormones of the adrenal cortex will make possible new approaches to the study of granulomas and may answer some questions which have long been apparent.

MAYO CLINIC.

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LXXXVIII

RHINOTOMY FOR EXPLORATION OF THE NASAL
PASSAGES AND THE ACCESSORY
NASAL SINUSES

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Inadequate exposure has long been recognized as a limiting factor in performing certain extensive surgical procedures in the region of the nasal passages and accessory sinuses. Each year in every large clinic two or three cases are seen with lesions in this area which are difficult to treat surgically by the usual intranasal procedures. These cases usually fall into one of three categories.

1. Intranasal tumors involving the neighboring sinuses that require liberal exposure both for the removal of the tumor and the control of subsequent bleeding.

2. Patients who have had repeated and often inadequate intranasal surgery with resultant loss of nasal landmarks, and excess scar tissue, with stenosis of the air passages.

3. Local osteomyelitis occasionally presents a third group of patients requiring increased intranasal exposure.

The following technique has been developed to provide improved exposure of the nasal passages and direct exposure of the nasal sinuses. This method of rhinotomy may be used first for exposure of the nares and nasopharynx, second for exploration of the maxillary and ethmoid sinuses, third for exposure of the orbital ethmoid sinuses and frontal sinuses.

Operative Procedure. General anesthesia is used. An oral intratracheal tube is passed and the surrounding pharyngeal area packed with gauze. The face is cleaned with the usual solutions, and sterile drapes are applied. Both alae nasi are elevated with a small retractor

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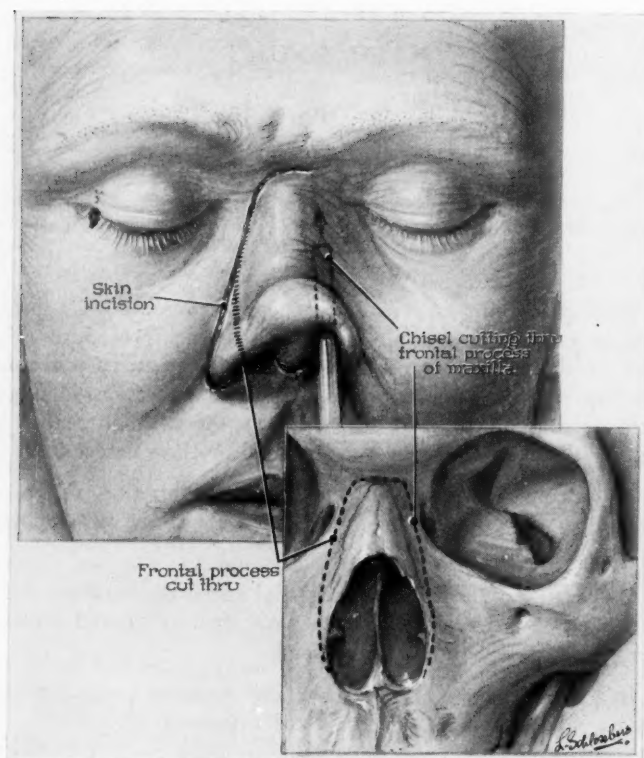


Fig. 1.

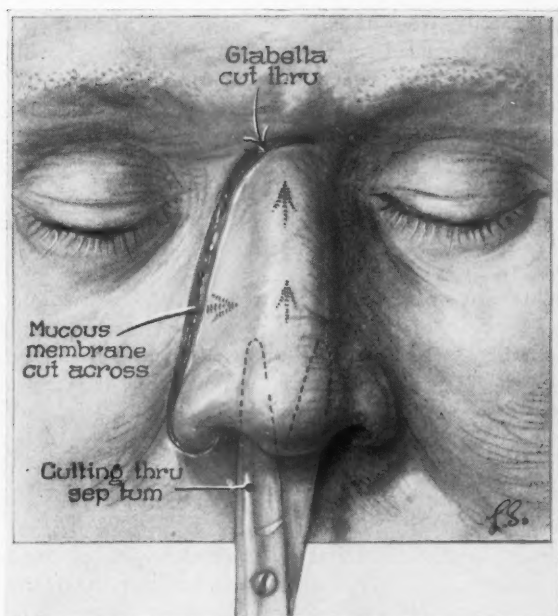


Fig. 2.

and the mucous membrane of the nose incised bilaterally anterior to the leading edge of the nasal bone (Fig. 1). The soft tissues and the periosteum are elevated over the frontal process of the maxilla and the lateral edge of the nasal bone on each side. Elevation is carried up to the nasofrontal suture. Mucous membrane and periosteum on the medial side of the nasal bones are elevated in the same manner. The frontal process of the maxilla is then chiselled free up to the nasofrontal suture on both sides. An incision is made on one side through the ala nasi and extended up the nasomaxillary fold to the level of the nasofrontal suture. It is then continued at right angles across the bridge of the nose to the upper angle of the severed frontal process of the maxilla on the opposite side. The bony bridge is cut across along the line of the nasofrontal suture with a chisel. This severs all the bones of the nose from their surrounding skeletal attachments. The base of the septum is then incised and the septum itself is cut across with scissors up to the level of the incision across the glabella (Fig. 2). The nose is reflected to the unincised side, using the soft tissue and periosteum of

that side as a hinge. It is wrapped in saline soaked gauze. Bleeding appears primarily from the lateral nasal and angular arteries and can be easily controlled on the lateral nasal wall. Small branches of the anterior ethmoid artery must be controlled when the mucous membranes are incised on the lateral nasal wall. More care is required in the control of bleeding from the septum. The septal branches from the superior labial artery which pass up each side of the columella should be clamped and coagulated. Two or three other small arteries on the septum will need to be similarly treated.

After all bleeding points are controlled a submucous resection of the remaining intranasal portion of the septal cartilage and the perpendicular plate of the ethmoid bone is performed (Fig. 3). Care should be taken to leave a small anterior column of septal cartilage to support the anterior portion of the nose when it is replaced. The septum may now be readily deflected from side to side, giving an excellent exposure of the ethmoid and sphenoid sinuses (Fig. 3), and also a very good intranasal view into the maxillary sinus (Fig. 4), if exploration of this area is indicated. If exploration of the frontal sinuses and the orbital ethmoid sinuses is necessary (Fig. 5), secondary incisions are made from the outer angles of the transverse glabellar incision up along the eyebrow. When the frontal sinuses are opened, the whole anterior wall of these sinuses should be removed, including the brow and the roof of the orbit as far posterior as the posterior wall of the frontal or orbital ethmoid sinuses so as to obliterate the dead space in these sinuses when the incision is closed. Slight diplopia, which may persist for several weeks, usually develops following this procedure. The incision over the frontal sinuses is then closed with subcutaneous catgut and interrupted silk skin sutures. A small penicillin soaked one-half-inch gauze pack is placed over the posterior wall of these sinuses and carried down into the nasal cavity.

The nose is replaced by first (Fig. 6) suturing the two portions of the septum together with interrupted sutures of No. 0000 atraumatic chromic catgut as far anterior as the columella. These sutures should all be placed before the first one is tied. The incision across the columella and the lateral nasal incision are closed with the usual subcutaneous catgut and silk skin sutures (Fig. 7). Care should be taken in replacing the nose to approximate the bony edges of the maxillofrontal process accurately. The approximation must be further secured after the incisions are closed by the application of an external stent of dental compound molded over the nose and held in place by adhesive strips and intranasal packing. If such approximation is not correct some slight stenosis of the anterior portion of

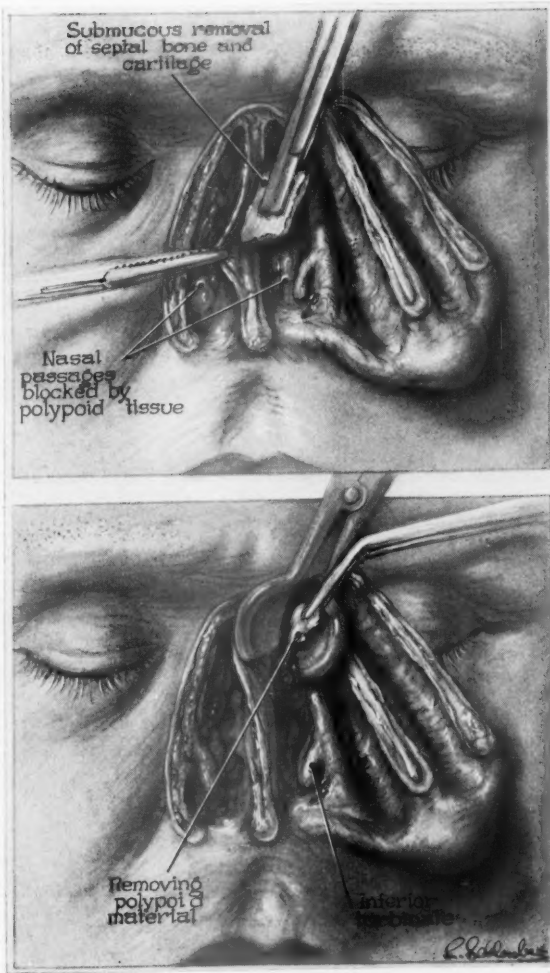


Fig. 3.

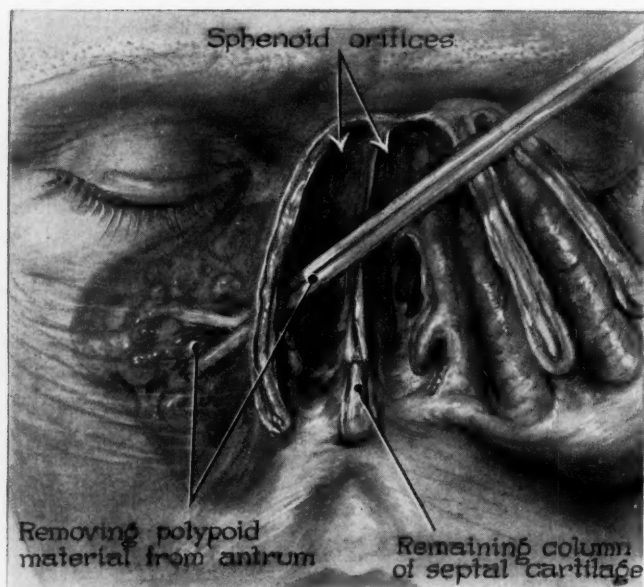


Fig. 4.

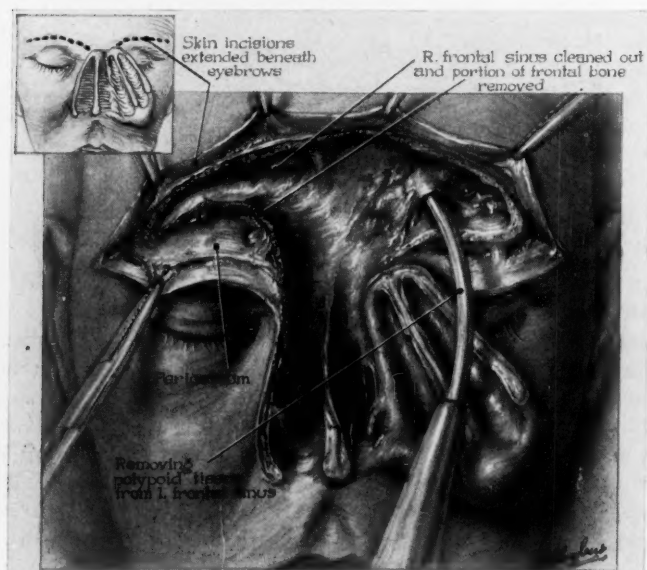


Fig. 5.



Fig. 6

the nostrils may result, especially on the severed side. The packs should be removed after 48 hours, at which time a pressure bandage is applied over the frontal sinuses. The stent remains in place from six to ten days.

The following cases are presented to illustrate the usefulness of the procedure. Cases 2 and 3 required only simple reflection of the nose, whereas Case 1 presented a more involved problem of severe infection of the frontal and orbital ethmoid sinuses.

CASE 1.—September 28, 1948. (Fig. 8, A and B).

The patient complained of a cough. The onset was in 1945 following the removal of nasal polyps. Following this he developed recurrent attacks of asthma. In the three-year period following the first operation, the patient had had two intranasal operations on the ethmoid sinuses and two radical antrum operations. In the six months preceding his examination at the Johns Hopkins Hospital, he had had constant asthma; at least one attack every 24 hours, in spite of the care of his allergist. On examination both nostrils were completely filled with polyps. There was a moderate amount of mucopurulent discharge seen in both nostrils. A portion of the middle turbinate had been removed on both sides and the membranes were so swollen that a satisfactory view into the nose could not be

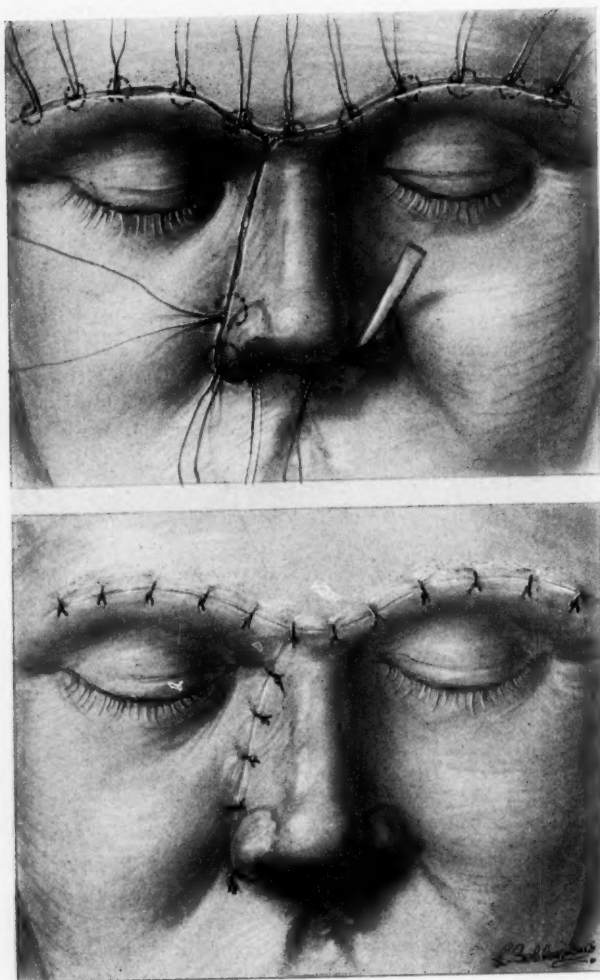


Fig. 7

obtained. X-ray films showed thickened membranes and polyp formation in the antra, thickened membranes in the frontal sinuses with generalized clouding. The frontal sinuses were extremely large.

After discussion of the contemplated operative procedure with the patient and his physician, Dr. Leslie N. Gay, Chief of the Department of Allergy, the patient was admitted to the hospital for rhinotomy.

Operation. (W. P. L. and J. E. B.) Pentothal anesthesia was used and the nose was reflected to the left. The septum was found to be extremely thick with marked hypertrophy of the membranes of both sides. A submucous resection had already been performed. The anterior ethmoid region contained some papillomatous appearing material and numerous small polyps. All of this tissue was removed along with the remainder of the middle turbinates, and the ethmoid cells were widely opened. Large openings were found into the maxillary antra both above and below the remnants of the inferior turbinates, apparently the result of previous surgery. These were choked with polyps. The periosteum over the right cheek was retracted and an opening was made into the right antrum. A large amount of pus, polyps and thickened membranes were removed. An excellent view was obtained of the maxillary sinus through the left middle meatus. This opening was enlarged and the maxillary sinus was exenterated. A large number of polyps and much polypoid membrane were removed. The window under the inferior turbinate was cleaned out and enlarged on both sides. Incisions were then made from the outer angles of the glabellar incision up over the brows on both sides. The soft tissue and the periosteum was reflected upward and both frontal sinuses were opened. The anterior walls were removed and the sinuses were found to be filled with pus, polyps and thickened mucous membrane. The orbital roof was removed down to the posterior wall of the frontal sinuses after elevating the periosteum from the orbital plate. Several large orbital ethmoid cells were found at the inner angle. These were opened, cleaned out, and the ethmoid cells around the frontal ducts were likewise opened, thus making a large opening from the frontal sinuses into the nose.

Penicillin soaked packs were placed in the cavities, the incision over the brow was closed and the nose was sutured in place. Its position was held by nasal packing in both nostrils and an external stent of dental compound. During the course of the operation, the patient received one pint of whole blood and 500 cc of 5% glucose. Penicillin and streptomycin were administered for five days sub-

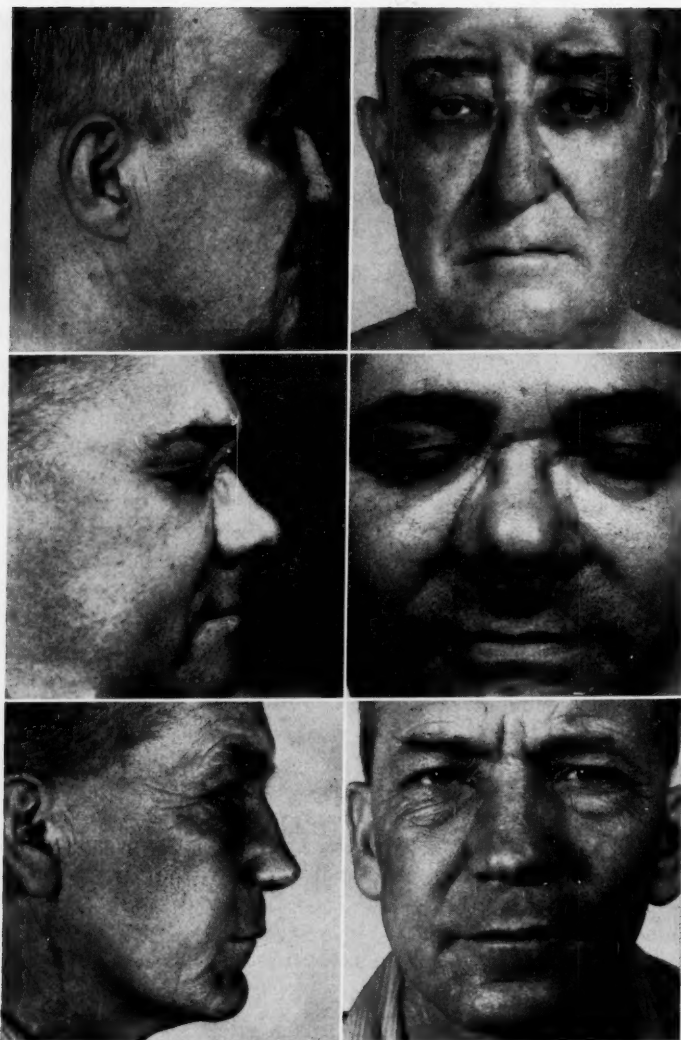


Fig. 8.—Postoperative photographs showing the cosmetic results of the rhinotomy operation. Photographs made between the third and sixth months postoperatively.

sequent to operation. His course was uneventful. His temperature did not rise above 100.5° F. and rapidly returned to normal. The packs were removed from the nose in 48 hours and an external pressure bandage was applied at that time over the frontal sinuses. The stent was removed on the seventh day at which time the skin sutures were removed.

Following operation, the patient's asthma disappeared within 24 hours and since that time, he has had only two subsequent asthmatic attacks; once from eating seafood, once from an upper respiratory infection. In the past three months, polyps have developed around the right ethmoid region and there has been a little mucoid discharge in that side of the nose. The left side has remained perfectly clean and now contains normal mucous membranes. The patient's general health has been excellent.

CASE 2.—(Fig. 8, C and D) The patient was admitted to Johns Hopkins Hospital through the Ear, Nose and Throat Clinic April 1, 1949; the operation was performed April 2, 1949.

The patient gave a long history of complete nasal obstruction. Nasal polyps had been present for 25 years. About 20 years ago he lost his sense of smell. He had had over 20 electrocoagulations of his nose and numerous polypectomies. He stated that he was willing to have anything done that might relieve his nasal obstruction. On examination, both nostrils were nearly completely occluded by synechiae, thickened mucous membrane and polyps. There was a small amount of discharge, mucoid in character in both nostrils. There were no normal landmarks visible. X-ray films showed clouding of the maxillary sinuses, the ethmoid sinuses and the sphenoid sinuses. The frontal sinuses were rudimentary. The patient had a hypertension of 190/130.

Operation. (J. E. B.) With the patient anesthetized with pentothal the nose was reflected to the left. A submucous resection was performed on the intranasal portion of the septum leaving a column of cartilage about 0.5 cm in depth at the inferior portion of the septum to form a supporting anterior column when the septum was resutured. The middle turbinates had previously been removed. The polyps were removed, the membranes were dissected away from the lateral nasal walls, and the remaining ethmoid cells were opened on both sides. The mucous membranes which were very scarred were almost 1 cm in thickness over the ethmoid region. The sphenoid orifices were enlarged on both sides. Openings were made into the maxillary sinuses through the middle meatuses. A large number of polyps and much thickened membrane were removed. Secondary

openings were made into the maxillary sinuses in the anterior portion of the inferior meatuses. The nose was replaced in the usual manner and held in position by internal nasal packing and external dental compound stent.

In spite of intravenous injections of 500 cc of whole blood during the first part of the operation, the patient's blood pressure continued to drop so that it was necessary to give a second 500 cc of blood, plus 500 cc of 5% glucose. After dropping to 120/80, his blood pressure began to rise and at the end of the operation it had reached 160/90. In this case there was a considerable loss of blood during reflection of the nose. Subsequent bleeding was readily controlled by direct pressure or by small packs placed in the operative field.

Postoperative Course. Twenty-four hours after operation the patient developed a chill, and the temperature rose to 104° F. The chest was clear. The nasal packs were removed and the patient's penicillin was increased from 300,000 to 600,000 units a day. Fever gradually subsided, temperature reaching normal on the fifth day. The stent was removed on the seventh day along with the sutures. The patient's course since that time has been uneventful. He has had no difficulty breathing through his nose. Membranes in the nose now look quite healthy. There is no unusual crusting, and breathing space has been excellent. One month after operation, the patient regained his sense of smell which he has retained since.

CASE 3.—May 24, 1949. (Fig. 8, E and F.)

The patient was referred from the Ear, Nose and Throat Clinic at the Johns Hopkins Hospital with a history of nasal obstruction on the right side of three months' duration with three or four episodes of severe epistaxis on the right side. On examination, the right nostril was completely occluded by what appeared to be a papillomatous growth. On posterior rhinoscopy a papillomatous appearing mass could be seen in the right side of the nasopharynx. X-ray films showed clouding of the right maxillary sinus, right ethmoid sinus and right sphenoid sinus. The frontal sinuses were rudimentary and appeared clear. The preoperative diagnosis was papilloma.

Operation. (J. E. B.) Pentothal anesthesia was used and the right external carotid artery was ligated. The nose was reflected to the left in the usual manner. The right nostril was seen to be completely filled with growth. A submucous resection of the intranasal portion of the septum was performed, leaving an anterior column of cartilage about 1 cm in length to support the anterior portion

of the nose. The growth which involved the inferior turbinate, the nasal wall of the maxillary sinus and the region of the middle and inferior meatus was removed. The inferior turbinate and the lateral nasal wall were removed. The middle meatus was exposed and the ethmoid sinuses opened. They were found to contain the same papillomatous material. A large amount of growth was removed from the nasopharynx on the right and on enlarging the sphenoid orifice on the right growth could be seen in the sphenoid sinus itself. No attempt was made to remove the growth from the sphenoid sinus. The antra appeared to be uninvolved, except for the medial wall. Bleeding was rather profuse but could be controlled under direct vision. Penicillin soaked packs were placed in the right antrum and the usual intranasal packing was used to support the nose. A dental compound stent was applied.

During the operation 1500 cc of whole blood was administered. Transfusion was started just before the operation and continued for an hour after the patient returned to the ward. Pathological diagnosis of tissue removed at operation showed papillary carcinoma.

The patient's postoperative course was satisfactory. Packs were removed in 48 hours without any unusual bleeding. The patient's breathing space had been restored. He was sent home for deep x-ray therapy. He has had no further complaints, bleeding or nasal obstruction.

CONCLUSION

An operative procedure is presented whereby maximal direct external exposure of intranasal spaces and the surrounding nasal sinuses may be obtained with minimal subsequent facial scarring and disfigurement. By reflecting the nose and performing a submucous resection on the remaining intranasal portion of the septum, direct view can be obtained of structures inadequately visualized in the usual intranasal surgical procedures. Subsequent septal perforation has not occurred. Necrosis of tissue on the reflected nose due to circulatory interference has not proved to be a hazard. The external cosmetic results are satisfactory, except in those cases requiring collapse of the frontal sinuses. Such cases will require subsequent restoration of the brow.

The operation is indicated in only a few carefully selected cases where the standard types of intranasal operations would not provide adequate exposure for safe removal of an extensive lesion.

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DIAGNOSIS AND TREATMENT OF MAXILLARY CYSTS

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Cysts of the maxilla are not unusual. They are met with most commonly by the otolaryngologist or the oral surgeon, since they may invade both fields at times.

Close co-operation between the two specialties is desirable and helpful in the diagnosis and treatment of certain of these conditions.

Since these cysts are of dental origin they are treated more often by the oral surgeon than the otolaryngologist.

Cysts of considerable size have been treated entirely through the canine fossa without use of the complete Caldwell-Luc technique which in many cases produces a much quicker cure than simple curettage and repeated dressing of the cavity through the canine fossa.

It is the purpose of this paper to describe three methods of treatment, each applicable to its particular type of case.

The three types of cysts to be described have certain characteristics in common:

1. They are located in the maxilla.
2. They are filled with the typical straw colored fluid containing cholesterol crystals.
3. They develop slowly.
4. They cause no symptoms until reaching such size as to cause deformity or paresthesia of branches of the fifth nerve.
5. Pain and a foul discharge occur if the cyst becomes infected.

Radicular Cysts. Radicular, or root, cysts occur at the apical ends of nonvital teeth, commonly from a granuloma in which epithelial rest cells are incorporated. The granulomas from which cysts arise are usually hollow and have become lined with epithelium which in turn has arisen from epithelial debris or rest cells. Radicular cysts are most common in the upper lateral incisor area.

One opinion¹ holds that these cysts represent an end stage of granuloma resulting from root infection and have an apical position. The vitality of the tooth involved is usually lost.

Other writers² state that since there are many peri-apical granulomas and also many Malassez' epithelial rests, one would expect to find cysts associated with them more often if they were the sole cause. Evidently some other exciting factor has not yet been discovered.

According to Gregory³ these cysts may be single or multiple. They form where the cells of the peridental membrane are stimulated to abnormal growth. A structure is thus formed which becomes cystic due to necrosis of the central cells of the mass and the accumulation of fluid in the center.

These cysts most frequently occur in adults and are relatively slow growing. When seen in the edentulous, they may be due to retained root fragments, which may have been small and unrecognized when the tooth was extracted.

Since radicular cysts may occur following injury to the root of a tooth, it is possible that carelessness in making the bony opening during a Caldwell-Luc operation might be responsible for root injury and possible cystic formation later on.

Follicular Cysts. Embryologically the dental follicle is derived from mesoderm and surrounds the embryonic tooth. At this stage the tooth itself consists of an enamel organ and dentine papilla.

The epithelial sheath, which separates the follicle from the enamel, and which forms the enamel of the tooth after the crown of the tooth is erupted, disintegrates, but fragments of it may remain in the follicular connective tissue.

The normal dental follicle is connective tissue with a lining of epithelium, the innermost layer of which is a columnar type of epithelial cell, called ameloblasts. Thus in the unerupted tooth we have a potential cyst, since there is a connective tissue sac with an epithelial lining.

Since these tumors occur in developing teeth, they are seen more often in young people. They arise during formation of the permanent teeth and later in life when the third molars are forming. As in the radicular cysts, they grow slowly and cause no symptoms until bulging of the bone, paresthesia, or pressure necrosis occurs.

When follicular cysts occur in the maxilla the swelling may be seen in the palate, or may encroach upon the maxillary sinus. If, as rarely occurs, it be bilateral, enlargement of the maxillary bones

causes facial deformity. With very large cysts, the bones become so thin as to give a crackling sound when pressure is exerted on them. Swelling of the bone at a point where a tooth is absent (unerupted) gives presumptive evidence of a cyst. This may be confirmed by x-ray examination.

Dentine, abnormal enamel, pulp tissue, and imperfectly formed teeth, may be found in addition to the typical cholesterol containing straw colored fluid. If infection has invaded the cyst, pus and blood may be present.

According to Lartschneider⁴ an inflammation of the dental follicle due to infection from adjacent teeth or by peritonsillar infection, stomatitis, gingival ulcerations or trauma, is the cause of dentigerous cysts.

Sprawson⁵ thinks that such cysts are all primarily radicular in origin, often formed in connection with septic deciduous teeth and in the same manner as the ordinary dental or root cyst connected with the septic root of a permanent tooth. He says further that such cysts migrate in the plane of least resistance where they may meet with a developing unerupted permanent tooth, which they surround, and in this way prevent its eruption. However, there are cases where deciduous teeth are not involved, and others where cysts arise from third molars which develop in the jaw at some distance from deciduous teeth.

Ivy⁶ states that the term dentigerous or follicular cyst should be applied only to those having the crown of an unerupted tooth in the cavity.

Suspicion that a dentigerous cyst is forming should be aroused when a permanent tooth fails to erupt at its usual time. X-ray films of the maxillary sinus may show a cyst of varying size occupying the anterior portion of the sinus and containing a tooth, the so-called tooth antrum.⁷

It is possible that some of the double antra described in the literature are in reality large dental cysts lying anterior to the true maxillary sinus.

Difficulty in mastication, or obstruction of the nasal cavity, may develop.¹ Secondary infection which occurs through the diseased pulp, or from an adjacent tooth, modifies the picture and may produce a fistula with offending discharge. Cysts may reach so large a size as to occupy the entire half of the jaw.

Early lesions are usually discovered after routine roentgenographic examinations. They are represented by localized areas of

rarefaction in the bone, often in connection with an unerupted, misplaced, or supernumerary tooth.

Median Maxillary Cysts. The median maxillary cyst arises from epithelial remnants of the nasopalatine duct, or from epithelial remnants which were trapped when centers of calcification united in the midline. Such cysts are usually of dental interest only; however, they may be located so as to involve structures of the nasal cavity or maxillary sinus. Median maxillary cysts are usually noticed by the patient late in life as a swelling in the region of the incisive foramen, except rarely where there may be destruction of the floor of the nose.

Diagnosis. The diagnosis of such nonmalignant cysts offers little difficulty as a rule. There must be a differential diagnosis between adamantinomas, odontomas, and malignancies such as carcinoma. When there is a swelling, painless or otherwise in the maxilla, x-ray films will show the character of the mass and whether it surrounds a tooth or springs from a granuloma on an infected root. Aspiration will show the typical clear yellow fluid containing cholesterol crystals or pus, and if the cavity be large, with very thin walls, a crackling sound will be elicited on pressure.

Subperiosteal abscess of the palate might give a misleading clinical picture, but x-ray examination will determine the true condition.

If malignancy had been present for some time, one would expect bleeding, tenderness, pain and the general debility associated with such conditions.

The source of the fluid content of these cysts is not known. It is evidently not a secretory product of the epithelial lining. It may be accounted for by difference in the osmotic pressure between the cyst content and the blood plasma and lymph analogous to that which occurs in the enlargement of subdural hematomas. Rosedale and Koepf² suggest determination of the interchange of phenolsulfonphthalein from the blood into the cavity and vice versa, as one method of learning something of the genesis of the fluid content of the cyst. The injection of certain dyes into the tumor might shed light on the problem by watching for their avenue of escape.

Diagnosis and location is facilitated by the injection of lipiodol into the maxillary sinus, and later into the cyst if necessary. It is best to fill the antrum first, as this procedure is usually sufficient to show whether the cyst communicates with the sinus. If a filling defect of the sinus is noticed after the use of lipiodol, it may be necessary to fill the cyst to determine its extent and location.

There are three methods of treatment of these conditions, based on their extent and location.

1. If the cyst is small, it may be handled purely as a dental problem. Under local anesthesia the front wall of the cyst is removed, the lining membrane is completely exenterated and the cavity dressed with gauze impregnated with tincture of benzoin or balsam of Peru. These dressings are changed twice a week until the cavity is obliterated.

In the case of median maxillary cysts, an incision is made in the soft palate over the tumor, the inferior bony wall removed, and the lining membrane exenterated. Dressings are changed twice weekly until healing is complete.

When cysts of some size occur in proximity to the maxillary sinus, a question arises as to whether simple removal of the cyst lining and repeated dressing are sufficient to cure the condition, or whether more radical surgery may be necessary.

2. If the cyst is a large one, with encroachment on the maxillary sinus, the Caldwell-Luc approach is used. In making the initial incision, if no teeth are present, or if teeth are not to be extracted, the usual Caldwell-Luc incision is preferable. If teeth are to be extracted, vertical incisions in the gingival border made well to each side of the cyst are to be preferred, as in this case a large flap can be left with which to close the defect. After retraction of the mucous membrane over the cyst, it is opened and the mucous membrane lining is completely enucleated. After removal of the lining membrane, the posterior wall of the cavity is examined and if it be strong enough, and there is no communication with the sinus, a nasocyst window may be made under the lower turbinate. This does not disturb the normal sinus lying behind and causes less postoperative reaction.

3. If, at operation, the posterior wall of the cyst is found to be egg-shell in character, or if the sinus behind it is infected, it is best to convert them both into one cavity and complete the Caldwell-Luc operation.

Simple irrigations via the maxillary window are all that is necessary postoperatively.

Whether the cyst be a radicular or dentigerous one, the treatment is the same. It is sometimes impossible to determine whether conservative or radical treatment is necessary until the operative procedure has started.

CASE 1.—*Radicular Cyst.* A male patient aged 43 had a bilateral Caldwell-Luc operation 15 years before examination.

About one year before he presented himself he developed swelling, redness, and tenderness above the left, first molar tooth. A dental x-ray film showed a granuloma of the left first molar with a cavity lying above it. Lipiodol was injected into the left antrum through the maxillary window with the patient lying on his left side to prevent escape of the oil. The resulting film showed the cyst-like swelling lying anterior to the sinus but not connecting with it. For academic interest only the cyst was then injected and another film showed its shape and exact location. At operation, the left first molar was removed. The cyst was then opened by the usual Caldwell-Luc incision and found to contain greenish yellow fluid. Its lining was exenterated and the cavity dressed with gauze impregnated with balsam of Peru. Dressings were changed twice weekly until the cavity had become obliterated.

Ten months following this episode identical symptoms occurred on the right side. The right antrum was filled with oil by the method described and the resulting x-ray film showed a large cyst-like cavity which had encroached on the antrum to a considerable extent, so that only a crescentic cavity remained posteriorly. The usual Caldwell-Luc incision was employed and the cyst found to contain greenish yellow fluid. The lining membrane was removed and since the cyst was too large to be treated by simple dressings, a nasocyst window was made. Convalescence was rapid.

CASE 2.—*Bilateral Radicular Cysts.* A female, aged 29, when first seen had deforming swellings over each maxillary region. There was no pain or tenderness but crepitus could be elicited on pressure. Primary x-ray films showed evidence of tremendous bilateral cyst-like swellings in both maxillary regions. Oil was not injected. Both cysts sprang from granulomas on roots of the second bicuspid teeth. At operation the walls of the cavities were found to be egg-shell thin. They were filled with greenish fluid containing cholesterol crystals. The posterior walls of the cysts were so fragile that they were removed entirely, thus converting two cavities into one. Large antral windows and the usual external closure completed the operation. Recovery was rapid.

CASE 3.—*Follicular Cyst.* This patient, aged 51, presented herself with the complaint of a foul discharge into the oral cavity. She was edentulous. Radiographs showed a maxillary cyst lying to the left of the midline. There was a fistulous tract leading from the cyst cavity into the canine fossa. The usual Caldwell-Luc approach was employed. The posterior bony wall of the tumor was absent

and only a membranous partition was present between the two cavities. This partition was removed, the thickened lining membrane was exenterated, and the two cavities converted into one. A large naso-antral window was made and the antro-oral wound closed.

CASE 4.—Follicular Cyst. A female, aged 42, was first seen with swelling and tenderness in the left bicuspid region. X-ray films showed a cyst-like cavity, containing a tooth, and encroaching on the sinus so that it was about 50% obliterated.

Operation was by the usual Caldwell-Luc approach. The tooth was removed, and the lining membrane of the cyst exenterated. Since the posterior bony wall was firm and the lining of the antrum appeared normal, a window into the cyst was made via the inferior meatus, and the external wound closed. There were no complications.

SUMMARY

Cysts of the maxilla are fairly common.

They present certain definite symptoms which make their differential diagnosis relatively easy.

Three methods of treatment are outlined, each applicable to a certain type of case:

First: Simple enucleation of the cyst lining and dressing.

Second: Enucleation of the lining and a nasocyst window.

Third: Removal of the posterior cyst wall and conversion of two cavities into one, followed by a naso-antral window.

Co-operation between the oral surgeon and otolaryngologist is desirable.

505 HUME-MANSUR BLDG.

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XC

NEBULIZED COCAINE AS AN ANESTHESIA FOR
PERORAL ENDOSCOPY

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AND

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Although this is a preliminary report covering the use of nebulized cocaine solutions in 257 consecutive endoscopic cases at the Veterans Administration Hospital, Bronx, New York, we have been gratified with the ease of administration, safety and degree of anesthesia obtained.

In May, 1948, King and Jones⁸ described a method of using 4% cocaine hydrochloride solution administered at five-minute intervals by laryngeal syringe for a total dose of 0.16 gm. This method was accompanied by coughing and gagging. The observation that the administration of aerosol penicillin or adrenalin did not provoke these reflexes suggested that cocaine solution might be used in the same manner. First, a No. 640 DeVilbiss nebulizer was employed and it was found to be practical but exhausting when pumped by hand. Then a compressed air unit was attached to maintain a continuous vapor and finally, oxygen was substituted, thereby adding a supportive measure in case of cocaine poisoning.

The apparatus consists of (1) an oxygen cylinder with humidifier, (2) rubber tubing, and (3) a DeVilbiss No. 640 nebulizer with a piece of wide rubber tubing 8 cm long attached to the mouth end. Three cubic centimeters of a 4% cocaine solution is measured and placed in the nebulizer. Additional equipment is a source of light, a head mirror, a laryngeal mirror, hot water, gauze and a laryngeal syringe with a curved tip.

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Read before the Section on Otolaryngology, New York Academy of Medicine, New York, N. Y., May 18, 1949.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.



Fig. 1.—Self-application of nebulized cocaine in the supine position.

From December, 1948, to May, 1949, in a series of 257 endoscopic procedures, only five required a general anesthetic. The remaining 252 consisted of 105 laryngoscopies, 53 bronchoscopies, 65 esophagoscopies, 20 combined and 9 aerostatic dilations.

In 1940 C. L. Jackson⁶ reported as the result of a questionnaire that for direct laryngoscopy about 50% of the operators applied swab applications of cocaine to the pyriform fossa (amount and strength not stated) and in addition the majority reported using some sort of spray or instillation. The same technique was resorted to for bronchoscopy and esophagoscopy.

Whalen¹² emphasizes that routine methods following fixed rules do not make for good anesthesia in endoscopy. Perhaps not, but we have had very little trouble in setting up standard orders. Our patients, all veterans ranging from 20 to 70 years of age, are seen in consultation. During the initial interview it is important to question the patient about cocaine idiosyncrasy, to reassure him and to

study his emotional status in order to estimate any variation from the routine.

Good anesthesia is contingent upon proper premedication. Some form of a barbiturate should be used as a pre-operative medication. Leshure¹⁴ in 1927 was the first to advocate its use prior to using cocaine.

Routine orders include a barbiturate, usually (one capsule of 0.1 gm) nembutal the night before, no food by mouth for six hours previous to surgery, nembutal (1 capsule of 0.1 gm) two hours before and repeated one hour prior to surgery. Thirty-five minutes before the operation a hypodermic is given containing 10-20 mg morphine and either 0.4-0.6 mg scopolamine for those under 45 years of age or atropine for those over 45 years of age. The patient is immediately taken by stretcher to the endoscopic room where he is placed in a chair in a screened off corner of the room, strapped in, given the nebulizer with 3 cc of a 4% cocaine solution aerosolized with humidified oxygen, and permitted to anesthetize himself. All we expect of this narcotized patient is to hold the nebulizer in his mouth with his lips closed around it. The oxygen is released at the rate of five liters per minute taking up to 20 minutes, during which time routine checks are made of the patient and the nebulizer is advanced gradually toward the epiglottis. At the end of this procedure it is necessary to decide on supplementation, depending on the patient and the procedure. At such times, in order to insure maximum anesthesia at a particular level, we have instilled by drop method up to 1.0 cc either onto the cord or through the glottic chink. If necessary, when doing an esophagoscopy, the same additional supplement may be dropped into the pyriform fossae. Finally, just before the operation there is delivered a modified "sermon on relaxation" as recommended by Jackson.

At this time it is important to emphasize that occasionally there may be good mucous membrane anesthesia but resistance due to neck rigidity. This renders proper glottic visualization difficult. Therefore, we have on several occasions given 5-8 mg morphine in 5 cc saline intravenously, thus permitting us to proceed immediately.

Jackson and McReynolds have previously very aptly summed up the requirements of peroral endoscopy to be safety, efficiency and comfort. We feel that our method of anesthesia definitely conforms to this triad of requisites.

Safety: We use only 4% cocaine hydrochloride solution; 1-3 cc nebulized and 0-1 cc dropped. Abramson¹ states that the DeVilbiss No. 640 nebulizer delivers particle radii from 0.3 to 2 microns. Findeisen,³ in his experimental work, confirmed by Van

Wigh and Patterson,¹¹ has found that the small particles in the 0.3-micron range are exhaled up to 65%, and those over 1 micron only 3%. Irritation of the mucosa and increase in absorption rate are caused by larger particles, which one can readily see removed by the curved portion of the nebulizer. We, therefore, have estimated that of the original maximum amount of 3 cc nebulized the patient receives less than 2 cc. This amount, if supplemented by dropping up to a maximum of 1 cc will have totalled 0.12 gm cocaine, falling far below the minimal lethal intravenous dosage of 0.2 gm. Bronchoscopy has been described as an ordeal and if one has a death it is an experience which is never forgotten.

We feel justified in advising the use of cocaine as the agent of choice for local anesthesia. Reference to the literature reveals the weight of opinion in favor of this drug, cocaine, derived from the leaves of *Erythroxylon coca*, known as benzoyl-methyl-ecgonine. Seevers,¹³ at a symposium on Anesthesia in Otolaryngeal Surgery in 1948 gave some statistics relative to the toxicity of local anesthetics. He stated that procaine and metycaine are the least toxic. In the second group comprising cocaine and butyn it is considered that they are 8-10 times more toxic than those in the first group. The third group, which is the most toxic, includes pontocaine which is 15-20 times more toxic than procaine, and nupercaine which is about 45 times more toxic. The use of pontocaine has caused an attack in asthmatic individuals or slight wheezing and it may also cause irritation of the throat which lasts for several days. At the same meeting he stated that there are probably more deaths from local anesthetics in this country than are published. He asked for a show of hands as to the number of toxic reactions observed during the past five years and judging from the response he estimated that there were between 30 and 40%. Jackson and McReynolds⁶ state that cocaine is admittedly the most universal and efficacious of the drugs used for local anesthesia. Rovenstine¹⁰ reports that with the extensive use of cocaine the incidence of fatal reaction is low and therefore it remains the most useful drug available today.

In general, the minimum amount of the lowest concentration of a drug that will give a satisfactory anesthesia should be used remembering that the toxicity increases in a geometric ratio. For example, a 2% solution which is four times more toxic than a 1% solution and not twice as toxic is more easily absorbed in a vascular area. A symptom of cocaine sensitivity not usually mentioned is the position of the thumbs in extreme tetany, both thumbs being drawn across the palms of the hands. Other signs and symptoms are that the patient complains of being uncomfortable, and there is restless

sighing, shallow breathing, clammy skin, excessive perspiration and twitching of the face and fingers. Reaction to sensitivity usually happens within 3-15 minutes and rarely after 30 minutes. Deaths from local anesthetics are cardiac in origin and result from convulsion of central involvement. In every operating room where cocaine is used a soluble barbiturate such as pentothal or amytal must be immediately available and given intravenously to control twitching and convulsions. A 2.5% solution of pentothal is given using just enough to control seizures, usually 3-5 cc.

Since more has been written about carcinoma of the lung in recent years and most writers stress the fact that the general practitioner should be more cancer-minded, it behooves us as endoscopists in making the diagnosis in bronchoscopy to report in detail the method, amount and strength of cocaine used. This information is lacking in the published reports. On examining the papers published in the Transactions of the American Broncho-Esophagological Association for the past 18 years one is struck by the fact that so few papers have been written about the sensitivity of cocaine in endoscopy.

Knowing more about the toxicity of these local anesthetics one should use the least potent and least toxic. We feel that if the amount and strength of cocaine is accurately measured and nebulized by oxygen, which is an antidote for cocaine poison, this is the ideal method of anesthetizing in endoscopy.

Efficiency and Comfort: The ease of performing an endoscopic procedure under this type of anesthesia is proof enough. One needs only to try it in several cases to be convinced. Patients who had been anesthetized by the old method readily report the tranquil administration with the absence of the cough and gag reflexes. For those patients unable to sit up nebulized cocaine may be administered just as easily in the supine position (Fig. 1).

Having found this method so practical we turned to the literature and found that Remorino⁹ reported using nebulized 2% pontocaine for bronchoscopy. Davis² also found aerolized pontocaine solution advantageous.

Very often in private practice the patient is sent to the hospital the morning of the day of operation and the doctor only sees him prior to the endoscopy. This procedure is wrong. We feel very strongly that the patient should be hospitalized the day before and given a thorough physical examination, being visited by the surgeon who has an opportunity to study him and become acquainted, thus relieving any fears in the patient's mind. At this time proper

pre-operative medication can be ordered, thus insuring a good night's rest before the operation.

In addition to its use in endoscopy we have administered nebulized cocaine in order to remove nasal polypi, as a preliminary for local tonsillectomies, to take specimens for biopsy from the nasal or pharyngeal cavities, to facilitate the instillation of endotracheal tubing and to instill iodized oil for a bronchogram. Recently while administering nebulized cocaine previous to a lipiodol procedure, a possible serious reaction was prevented when we were able to detect toxic effects in the patient who had received less than 1 cc of a 4% cocaine solution over a ten-minute period. We, therefore, like to consider this method a sensitivity test if one keeps in mind the impending symptoms and signs of cocaine allergy.

SUMMARY

1. Nebulized cocaine has been proposed as a routine method for peroral anesthesia. This may be used as a preliminary anesthetic in some cases or a definitive one in others.

2. This method of anesthesia was used in 257 endoscopic cases at the Veterans Administration Hospital from December, 1948, to May, 1949.

3. The preliminary preparation of the patient for an endoscopic examination and the administration of the local anesthesia is described.

4. The total amount of the anesthetic agent is controlled and recorded in each case.

5. Widened application of nebulized cocaine anesthesia is suggested.

6. It is proposed that nebulized cocaine be used as the safest practical method of detecting cocaine sensitivity in a patient.

Note: Since this article was submitted for publication there have been over 600 patients anesthetized by this method and the results have been entirely satisfactory.

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Clinical Notes

XCI

OBJECTIVE TINNITUS

REPORT OF A CASE

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The role of vascular injuries as an etiological factor in objective or audible tinnitus is well known. Numerous cases have been reported and many more seen in which a vascular lesion could be heard by an outside listener as well as the patient. Aneurisms and arteriovenous fistulas are the most common causes for these vascular disturbances. A rather striking and unusual case of objective tinnitus was recently seen in this hospital.

Five days prior to examination this forty-two-year-old man experienced an accident while sleep-walking. He awoke in the morning to find he had upset a chair and bruised his left ear and the left side of his head. A small amount of dried blood was present on the left auricle. Some 12 hours after this awakening he noticed a whistling noise in both sides of his head, slightly more marked on the left side. The noise changed tone depending on his activity; the more he exerted himself the louder and faster the whistle. When he was quiet the whistle changed to a soft whir. On several occasions the noise seemed to stop for many minutes. He had occasional dizzy spells on standing up. His entire head felt full, but his vision and hearing seemed normal. The patient was comparatively little bothered by the constant whistling in his ear.

Examination revealed a well-built man, rational, oriented, and co-operative, in no apparent discomfort. His past as well as his family history were not contributory. His blood pressure was 140/80. The heart and lungs were normal. Neurological examination on several occasions revealed no abnormality in any of the cranial nerves or reflexes. Blood studies and urinalysis were normal.

From the Thayer Hospital, Waterville, Me.

Examination of the nose and throat was within normal limits. A small laceration was present on the left auricle and a tender area in the left parietal region.

At a distance of six inches from either ear, one could hear clearly a sharp whistle synchronous with the patient's pulse. This whistle was not audible in the frontal or occipital areas but seemed to emanate from both ear canals. With a stethoscope the sound was most prominent in the left temporal fossa. There was no palpable thrill. The whistle changed pitch with change in the patient's activity such as lying down or exercising. It could be made to disappear by pressure over the left carotid artery and over the temporal fossa. There was no evidence of a bruise in the left temporal region. Although the whistle was slightly louder to the patient on his left side, it seemed equally loud on both sides to a number of observers. There was no visible pulsation in the head. The audiogram showed normal hearing.

After several weeks of study during which the patient was ambulatory, he noted a gradual decrease in the loudness of his audible tinnitus. An arteriogram was interpreted as a thrombosis in the anterior branch of the superficial temporal artery. After several months of persistent objective tinnitus the patient was scheduled for ligation of his superficial temporal artery. On the day prior to the scheduled surgery, the whistle spontaneously ceased and has not recurred during the last ten months.

Several interesting aspects are discerned in this case. Although the audible tinnitus was quite loud, far louder than any subjective tinnitus as measured by masking, and although it persisted constantly for several months, the patient was never particularly bothered or distracted by the noise. One would naturally assume that so loud and persistent a whistle would become most disturbing to the individual. However, such was not the case. The personality seems to tolerate and adjust to extrinsic sounds much more readily than intrinsic ones (nonvibratory tinnitus). This becomes more apparent when we realize how comparatively innocuous are the common street noises and occupational sounds, and how bothersome a rather weak subjective tinnitus is at times.

Of further interest is the transmission of sound in this case. The vascular whistle produced in the left temporal fossa was equally audible to the patient and examiners in both ears. The sound seemed to emanate through both ear canals and was objectively inaudible in the rest of the head unless a stethoscope was placed in direct contact to the left temporal area. The tinnitus could be made to later-

alize to either ear if it were occluded. The vascular thrombosis acted as a tuning fork, and the sound produced was conducted by the skull.

One is safe in assuming that aneurisms, thrombi and similar disruptions in the intracranial fossa produce abnormal sounds in the area affected. If the vessel or the area is in contact with the skull, as in this case, the newly introduced sound becomes audible and is called a "vibratory tinnitus," being either subjectively or even objectively heard. If, however, the source of the new sound is surrounded by soft tissue or is not in contact with a part of the skull that acts as an adequate conductor, the patient is not aware of it, although it is physically present. Such is the case in most intracranial vascular abnormalities. Consequently it is quite difficult to detect them early. Von Békésy's profound reasoning offers many new channels of thought and investigation when he considers how efficiently the temporal bones have been placed in the skull so that they are acutely sensitive to outside sound and yet most effectively insensitive to the many sounds produced by the noisy organs inside the body itself. That intracranial vascular noises and introduced abnormalities will some day be detectable by sound equipment is fairly certain, and it is worth while to direct investigation into this channel.

SUMMARY

1. A case of audible tinnitus is presented.
2. Extrinsic sounds are generally better tolerated than intrinsic sounds.
3. Audible tinnitus can be an important diagnostic symptom. Investigations are worth while for the detection of sounds produced by intracranial vascular abnormalities.

THAYER HOSPITAL.

XCII

FOREIGN BODIES OF THE LARYNX

WITH REPORT OF AN UNUSUAL CASE

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According to Clerf³ it was during the early nineteenth century that much information was accumulated and definite views were formulated concerning foreign bodies of the air passage. At this time many of the symptoms, physical signs and other important observations were made and these are still fundamentally sound. Ryland¹⁶ in 1838 made the following statement:

"How many persons have perished perhaps in an instant, and in the midst of a hearty laugh, the recital of an amusing anecdote, or the utterance of a funny joke from the interception at the glottis of a piece of meat, a crumb of bread, a morsel of cheese, or a bit of potato, without a suspicion on the part of those around of the real nature of the case . . . when the actual cause of death lay quietly and unobserved at the door of the windpipe of the deceased."

It was Gross⁵ in 1854 who stated that as early as 1690 Muys reported the death of a 7-year-old child by suffocation after aspirating a bean.

Since the early nineteenth century there have been numerous reports both in the foreign and the American literature of foreign bodies of the larynx. Some of these cases are very interesting and bear brief mention.

Jowett¹² and Myers¹⁴ each reported instances of foreign bodies aspirated as a result of grand mal epileptic seizures. In the first instance a piece of a bone paper knife was lodged in the larynx. The bone knife had been thrust between the teeth of the patient by a well-meaning bystander to avoid biting of the tongue during the convulsion. Myers' case was that of a 42-year-old patient who aspirated a partial upper dental plate. This mishap also occurred during an epileptic attack.

The case of a 2½-month-old infant with a screw in the glottic aperture was reported by Tremble.¹⁸ Tuohy and Pemberton¹⁹ found

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Read before the Section on Eye, Ear, Nose and Throat, State Medical Association of Texas, Annual Session, San Antonio, May 3, 1949.

a wad of chewing gum in the pyriform fossa in a 9-year-old boy after general anesthesia. They assumed it had been regurgitated from the stomach, since nothing was noted at the time of beginning anesthesia.

Diggle's case⁴ was of a patient who had aspirated the "eye" component of a "hook and eye." The "eye," being U-shaped, was found fitting snugly over the left vocal cord; one limb of the U lay in the laryngeal ventricle and the other lay on the subglottic surface of the cord. The smooth joining part of the U looked medially toward the opposite cord.

Iglauer⁸ reported the case of a metal chip embedded in the laryngeal mucosa; Hunter⁷ found a metal rivet in the larynx of an 11-month-old infant. Over a period of four months the latter case had been variously diagnosed as: laryngismus stridulus, bronchopneumonia, and diphtheria. Such a case emphasizes the great importance of a careful history and routine x-ray examination.

Animal and vegetable foreign bodies have been found by Robbins¹⁵ and Brewster.¹ Robbins found cases involving echinococcus, ascaris, trichina and leeches. Brewster's patient fractured a rib in a paroxysm of coughing when a piece of walnut became stuck in the larynx.

We have been unable to find reported in the literature available to us any case similar to ours. It involved a coin lodged in both laryngeal ventricles and resting on the vocal cords in a plane perpendicular to the vertical axis of the body. The unusual element in the case is not so much the nature of the foreign body, as the plane at which it became arrested. As will be seen later, a foreign body which stops in the larynx usually becomes fixed in the plane of the vertical axis. This was the plane of lodgment of the metal rivet, screw, dental plate and metal chip in the cases referred to above. The sagittal plane is usually assumed by a descending laryngeal foreign body. Chiefly responsible are the funnel shape of the larynx, the motion of the vocal cords, and the narrowing at the glottic chink.

Judge¹³ reported the case of a soldier who had a shell fragment (1 cm x 2 mm) penetrate the right side of his neck and lodge in the tissue in the vicinity of the opposite laryngeal ventricle. This, however, is not analogous to the present case.

Jackson and Jackson⁹ have reported 3,000 cases of foreign bodies of the food and air passages but tabulated no such case as that to

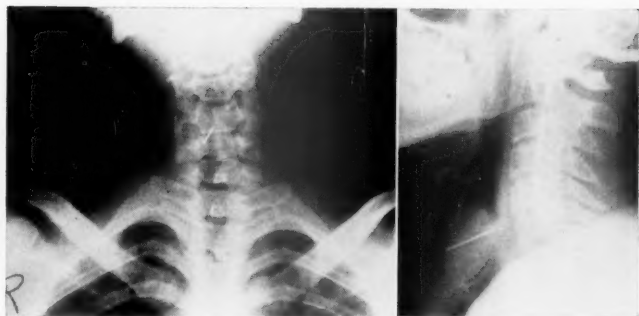


Fig. 1.—X-ray films illustrating the position of a straight pin lodged in the larynx; both A P and lateral views.

be presented, and according to C. L. Jackson¹¹ they have not seen such a case since that report was made.

Diagnosis of laryngeal foreign bodies, as outlined by Jackson and Jackson,⁹ depends on a careful history, laryngeal symptoms manifested, x-ray examination and laryngeal examination. History will indicate the patient had some foreign object in the mouth. Laryngeal symptoms include part or all of the following: discomfort or sense of contact, pain, hoarseness, croupiness, cough, aphonia, hemoptysis, wheezing, dyspnea, cyanosis and stridor. Symptoms of discomfort may become less pronounced if the patient tolerates the foreign body for a long period. The importance of x-ray examination will be pointed out presently. Preliminary laryngeal examination should be carried out with a laryngeal mirror in adults. A direct laryngoscopy is essential for infants and children. In any given case of suspected laryngeal foreign body, one should never make a negative diagnosis by deduction, but always look to be sure.

To understand the diagnosis and mechanics of a foreign body of the larynx one must understand the anatomy. Of particular interest on each side of the larynx are the false vocal cord, ventricle of the larynx, and the true vocal cord. Movement of the vocal cords is primarily in the horizontal plane when the subject is in the upright position. The cords adduct or approximate each other in the acts of phonation, coughing, etc., and abduct or separate in respiration. The glottic chink, then, is the narrowest part of the larynx to be traversed by a descending foreign body. As the narrowest point, it would be expected to mold the foreign body, or at least to direct it to a sagittal plane as opposed to a horizontal plane. This,

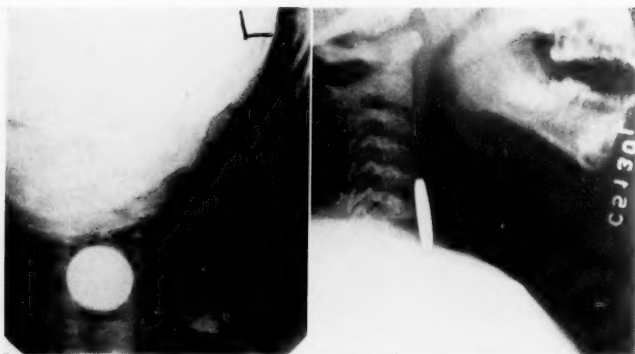


Fig. 2.—X-ray films showing typical position of a coin arrested in the upper esophagus. A P and lateral views show the plane to be opposite to that involved in laryngeal foreign bodies.

in fact, is the case in most instances, assuming the foreign body is not coughed out or exploded back into the pharynx by the bechic blast.

Figure 1 is shown to illustrate this typical position. This is one of our cases involving a straight pin caught in the larynx. Had the object which lodged in the larynx been flat, such as a safety pin, the usual position would also be in the sagittal plane, i.e., parallel with the axis of the larynx.

By way of contrast, in Fig. 2 the x-ray films show the typical position assumed by a coin lodged in the upper esophagus of an infant. In this situation, the cricopharyngeus muscle sling, or upper "pinch cock" of the esophagus, being the narrowest point, determines the position. Since its least diameter is in the anteroposterior plane and its greatest is in the coronal or side-to-side plane, the coin lodges in the coronal plane.

These classical positions of lodgment are important in a differential diagnosis. From the x-ray picture alone one is able to state whether the object lies in the esophagus or larynx.

At this point, the admonition of Chamberlain and Young² regarding x-ray diagnosis should be noted. They emphasize the fact that in some individuals calcification of the laryngeal cartilages takes place in early adult life. Calcifications may occur as early as the twentieth year in males and the twenty-second year in females. Such findings on x-ray examination may confuse the diagnosis as to lar-

yngeal or upper esophageal foreign bodies. They refer to Jönsson's suggestion of employing the Valsalva maneuver. This action inflates the hypopharynx and laryngopharynx at the time of making the x-ray picture.

Having reviewed the anatomy of the larynx and the x-ray films of typical findings, we come to the exception to the rule. Figure 3 shows films from the unusual case we are presenting. The coin is seen to be lying in the larynx in the horizontal rather than the vertical plane.

REPORT OF A CASE

The case is that of a merchant seaman, white, aged 55. The chief complaint on July 11, 1948, was that he could not breathe well and was very hoarse.

According to his history, the patient had aspirated a dime on July 5, six days earlier, while performing amateur magic tricks to amuse fellow members of the crew on board ship. Ordinarily the trick consisted of making the dime disappear by concealing it behind the lower lip and then pulling another dime, which had been concealed in the hand, from behind the ear. Thus the coin appeared to be swallowed and then pulled out the ear. On this occasion, however, the dime disappeared into the patient's larynx and initiated a severe paroxysm of choking. During the remaining five days of the voyage, the patient was extremely hoarse and was unable to do his work. When he moved into certain positions he could not get his breath. He was confined to his bunk where he had to sleep in a sitting position. Past history and review of systems were of no consequence except for shrapnel wounds of the abdomen and left leg sustained in World War I. Routine hospital laboratory studies, including the Wassermann reaction, showed normal findings.

Physical examination at Jefferson Davis Hospital revealed a 55-year-old white man of "stocky" build, speaking with a very hoarse voice, not acutely ill, and not in respiratory distress. The examination was not otherwise remarkable except for the larynx. It was noted on indirect mirror examination of the larynx that there was marked brawny edema of the false vocal cords, aryepiglottic folds and the small portion of the true vocal cords visible posteriorly. Lying anteriorly on the true cords below the false cords and extending laterally on each side into the laryngeal ventricles was a shiny silver coin, apparently an American ten-cent piece. The anterior two-thirds of the glottic chink, including the anterior commissure, was obstructed by the coin. The available airway remaining was the small space between the vocal cords and vocal processes poster-

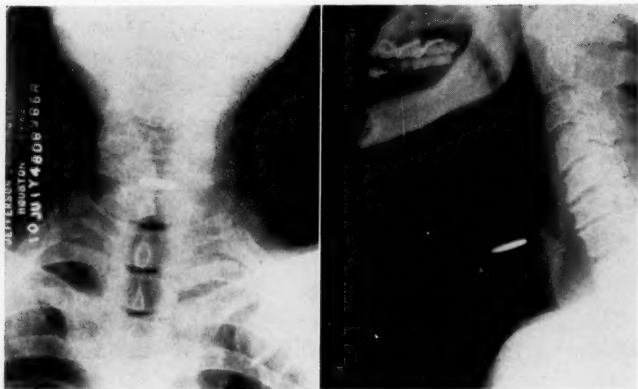


Fig. 3.—X-ray films showing in A P and lateral views the unusual position assumed by a dime. It had been lodged between the true and false cords for six days.

iorly. On attempts at phonation the coin did not move but seemed to be fixed.

Management of the case was as follows. An elective low tracheotomy was performed under local anesthesia and a No. 8 tracheotomy tube was inserted through the incision of the third and fourth tracheal rings. After removal of the metal inner tube, a No. 28 French rubber catheter was introduced through the tracheotomy tube to the bifurcation of the trachea at the carina. This procedure insured a free airway no matter what took place in the trachea above.

During the process of local anesthesia of the pharynx and larynx with the topical application of pontocaine and cocaine, the coin became dislodged and moved into the subglottic area. It was arrested in this area by the tubing already lying in the trachea. Using a Jackson anterior commissure laryngoscope and "alligator" grasping forceps, the coin was readily removed by mouth from the subglottic area. Had the coin remained in the original position, the angle biting biopsy forceps would have been used for grasping and removal. There was considerable edema of the true vocal cords visible where the coin had lain against them.

For the first 48 hours postoperatively the patient could not tolerate plugging of the tracheotomy tube even momentarily. It was removed, however, on the fourth day and he made an uneventful recovery. The patient is now back on the high seas having sworn off tricks of magic.

In discussing the management of this case the question that comes to mind is whether or not a tracheotomy was indicated. Our line of reasoning was somewhat as follows. General anesthesia in a foreign body case of this type might prove disastrous. Local anesthesia seemed the method of choice. With the coughing and gagging incident to anesthetizing the larynx locally, plus the local deadening effect, the coin might become dislodged; even though it had remained in place in the larynx for six days preceding. As already pointed out, this is actually what did happen.

As best the relations could be estimated pre-operatively, a dime seemed to be approximately the same diameter as the adult male trachea of a stocky individual. Later measurements proved this assumption to be correct. A dime measures 18 mm in diameter. According to Morris¹⁷ "Human Anatomy," the trachea in the male over 20 years of age averages from 16-22.5 mm when distended. In regard to the trachea, Chevalier Jackson¹⁰ states: "The respiratory movements are an enlargement of lumen combined with an elongation, on inspiration, and a reciprocal diminution and shortening on expiration."

It is possible, if not highly probable, that this "milking" action would have wedged the freed 18-mm coin into the tracheal lumen so as to occlude completely its diameter of 16-22.5 mm. At such a time the introduction of a bronchoscope or performance of an emergency tracheotomy would have been extremely difficult, if not impossible, with the patient thrashing about wildly. Even if a tracheotomy were possible, one could not be assured of getting below the obstruction to establish an airway.

Possibly this whole line of reasoning was erroneous and our fears were entirely ungrounded. However, two facts may be offered in support of it. First, the human equation: We felt that in our hands this approach would be best. Second, the patient is alive today.

SUMMARY

A few remarks on history of foreign bodies of the larynx have been cited and interesting cases from the literature reviewed. In this group, and the 3,000 cases from the Jackson Clinic, no case paralleling the present one was found. Diagnosis of laryngeal foreign bodies was seen to depend on history, symptoms, x-ray and laryngeal examination. Differential points of x-ray diagnosis of foreign bodies of the larynx and upper esophagus were noted after reviewing anatomy of the larynx. The case of a merchant seaman was presented. While at sea, he had a dime lodged in his larynx for six days. It was found lying on the true vocal cords extending laterally into

both laryngeal ventricles; hence in a plane perpendicular to the long axis of the body and contrary to the usual plane of arrest in such a case. After elective tracheotomy to insure an airway, the dime was removed from above using an anterior commissure laryngoscope and alligator forceps. Discussion of the management of the case was given.

The author wishes to express appreciation to Dr. William Skokan and Dr. M. S. DeVore for their assistance in the preparation of this article.

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XCIII

TRACHEOTOMY IN BOTULISM

REPORT OF A CASE

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AND

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This paper reports a case of botulism in which tracheotomy was done in addition to the customary forms of therapy. No previous similar case has been found in the literature.

Botulism has been recognized as a type of food poisoning since 1820 when the disease was first described by the German poet physician, Justinus Kerner.¹ *Bacillus botulinus* was discovered by van Ermengen in 1897. He proved that botulism was caused by the ingestion of foodstuffs containing the toxoid liberated by botulinus.²

Botulism is an intoxication rather than an infection. Unlike most bacteria dangerous to man, *B. botulinus* cannot live in the human body. Its pathogenic effect is produced by the action of the toxin liberated in foods. The symptomatology and course of the disease are determined largely by the amount of ingested toxin.

Investigations show that the toxin acts peripherally and not directly upon the central nervous system. Dickson and Shevsky³ demonstrated that the essential action of the botulinus toxin was a paralysis of the motor nerve end-plates of the voluntary nervous system and a blocking of the motor and secretory fibers of the parasympathetic portion of the autonomic nervous system. Recently Torda and Wolf^{4, 5} proved that the synthesis of acetylcholine decreased in the presence of the toxin and they suggested that the decreased acetylcholine synthesis was mainly responsible for the neuromuscular phenomena involving the parasympathetic system. The toxin exerts no effect upon the nerves of special sense, the sympathetic division of the autonomic system, or the sensory fibers of the peripheral nerves.

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The symptoms of botulism usually develop 12-24 hours following the ingestion of tainted food. In approximately one-third of the cases the local action of the spoiled food rather than the action of the toxin itself upon the gastro-intestinal tract results in early nausea and vomiting. Disturbance of vision as manifested by blepharoptosis, mydriasis, diplopia and dimness of vision are often the first symptoms. Fatigue is noted early and is followed by progressive muscular weakness. By then there is marked dysphagia, dysarthria and dyspnea. In describing his own affliction, Stiles⁶ commented upon the marked mental irritability experienced when he was unable to speak clearly or to swallow viscid pharyngeal mucus. Profuse exudation in the nose and throat simulating a diphtheritic membrane is often present and has led to difficulty in differential diagnosis.⁷ Constipation and inability to urinate are almost always present in botulism. The sensorium is usually clear until the terminal stage of the disease. Although death has occurred within 18 hours following the ingestion of the toxin, usually the symptoms attain their climax by the eighth or tenth day. At that time the patient is often markedly apprehensive because breathing becomes almost agonizing. He literally fights for air because of the weakness of his respiratory muscles and inability to clear his throat of viscid mucus. Bronchopneumonia frequently results from aspiration of secretions.⁸ Death is due to respiratory failure. Some observers have attributed death to cardiac failure but experimental evidence and experience in human outbreaks have shown that the heart may beat for several minutes after breathing has ceased.^{9,10} The case mortality rate in botulism is 65%.¹¹

Experienced observers stress the importance of early diagnosis based on history and objective findings so that botulinus antitoxin can be given early.¹² Another major therapeutic measure in the more severe cases is artificial respiration. In 1923, Edmunds and Long¹³ demonstrated in animals that it was always respiratory failure that killed and that if respiration by artificial means was instituted, the life of the animal could always be prolonged. On the basis of their experimental work they suggested that "in cases of human botulism, when the respiration shows signs of failure, artificial respiration should be instituted—if necessary, by means of bellows and a tracheal cannula." Following the advent of the respirator, clinicians suggested its use in cases of respiratory failure in botulism.¹⁴ During an outbreak of 16 cases of botulism in Seattle in 1939, Watson¹⁵ demonstrated the indispensability of the respirator in the treatment of the more toxic cases with respiratory paresis. Since then

others have emphasized the therapeutic importance of the respirator.¹⁶

In analyzing the case histories, one is impressed with the frequency of grave choking attacks resulting from obstruction produced by the aspiration of the viscid pharyngeal secretions. Watson,¹⁵ after observing his patients, aptly remarked, "It was truly pathetic to observe the distress with strangulation and cyanosis which accompanied the paroxysms of coughing in an attempt to clear their throats." Often the only significant postmortem finding in the fatal cases is gross atelectasis.^{10, 15}

The problems of management of the botulism patient, therefore, are similar to those of bulbar poliomyelitis patients who have respiratory distress because of pharyngeal pooling of mucus. During the 1946 epidemic of poliomyelitis in Minneapolis, Minnesota, Priest, Boies and Goltz¹⁷ commented on the efficacy of tracheotomy in properly selected cases of bulbar poliomyelitis. As the result of this experience, tracheotomy was performed upon a patient suffering from botulism in 1948.

REPORT OF A CASE

A thirty-two-year-old male Negro was admitted to the contagion service of the Minneapolis General Hospital on December 23, 1948, following transfer from a private hospital where a reserved diagnosis of bulbar poliomyelitis had been made.

The patient was well until 7:00 p. m. on December 19th when he arose to prepare for his night employment. At that time he noted double vision; however, he reported for work. The diplopia persisted, and on the following day he noted drooping of the right eyelid. A private physician was consulted on that day and the patient was instructed to return if the symptoms continued. The patient worked the night of December 20th during which time he noted drooping of both upper eyelids, the onset of generalized weakness and slight difficulty when swallowing. He returned to his physician the following day because of the persistence of the original symptoms. In addition, the patient noted increased weakness and a slight slurring of speech. He was hospitalized in a private hospital on December 22nd, where the diagnosis of possible poliomyelitis was made and the patient subsequently was transferred to the contagion service of the Minneapolis General Hospital.

In addition to the above history, the admitting resident physician elicited the history of ingestion of spoiled food approximately 12 hours prior to the onset of diplopia. The patient had purchased beef kidney on December 16th and prepared a meat vegetable stew

which was stored unrefrigerated. On the morning of December 19th, when he ate approximately one and one-half cups of the stew, he realized that it tasted "spoiled" and the remainder of the food was discarded. The past history was negative except for primary syphilis in 1945, which was adequately treated by a bismuth mapharsen regimen.

Upon admission, the patient was very weak and the examining interne noted that the patient "spoke as though his tongue were swollen." The patient preferred the prone position for when he turned on his back he had difficulty in breathing. The temperature was 99° F. orally, the pulse rate 80 beats per minute, the respiratory rate 16 per minute, and the blood pressure was 130 mm of mercury systolic and 100 mm of mercury diastolic. Bilateral ptosis and weakness of all extraocular muscles were present. Examination of the mouth revealed the accumulation of a considerable amount of thick, tenacious mucus and the tongue appeared flaccid and was noted to drop back in the oropharynx when the patient was supine. The muscles of the soft palate appeared sluggish and the patient had much difficulty in clearing the viscid secretions from the pharynx. He had difficulty in maintaining his head in the erect position and marked weakness of both sternocleidomastoid muscles was noted. Examination of the chest revealed poor respiratory excursions with apparent weakness of both diaphragmatic and intercostal components. Uniform muscle weakness was noted in all four extremities. A questionable increased tympany was noted upon percussing the abdomen and the bowel signs were diminished upon auscultation. Except for the slight blurring of vision all the nerves of the special sense were functioning normally. The Babinski, Kernig and Brudzinski tests were negative and sensation was equal bilaterally to light touch and pin prick.

The immediate laboratory examinations were as follows: Spinal puncture performed on the day prior to transfer to the Minneapolis General Hospital showed clear fluid and absence of cells. The hemoglobin was 108% (Sahli) and the leucocytes numbered 5,700 per cmm of blood, 67% of which were neutrophils, 26% lymphocytes, 5% monocytes and 2% eosinophils. The results of urinalysis were normal and the CO₂ combining power was 50 mg%. The Kline test for syphilis was negative. A throat culture failed to reveal either hemolytic streptococci or diphtheroids.

In view of the history of ingestion of spoiled food and the presence of the typical signs and symptoms of the disease, the diagnosis of botulism was made.

Clinical Course. Four hours after admission the patient became restless because of severe strangling when he attempted to swallow. Frequent suction of the viscid secretions was required to prevent the aspiration of the material into the respiratory tract. Thirty thousand units of combined type A and B botulinus antitoxin in 500 cc of 5% glucose in distilled water with one minim of epinephrine was administered intravenously. Penicillin in the dosage of 100,000 units every six hours was given intramuscularly. On the following morning, December 24th, the patient was extremely apprehensive and had obvious respiratory embarrassment. Direct laryngoscopy was performed and a polythene intratracheal tube was introduced. Following suction of thick mucus from the trachea, oxygen was administered with a mask. One cubic centimeter of coramine was given intravenously and the patient was placed in a respirator. The patient responded well after being in the respirator and receiving oxygen for a period of six hours although repeated suction of both the oropharynx and the intratracheal tube was necessary to prevent choking attacks and aspiration of the mucus. Since it was obviously impossible to leave the intratracheal tube in place while waiting an indefinite time for recovery from pharyngeal paralysis to take place, a tracheotomy was advised. The intratracheal tube was attached to a Heidebrink gas machine and the patient's respiration was controlled by positive pressure pumping of the oxygen bag. He was removed from the respirator and a tracheotomy was performed under local anesthesia. Following tracheotomy he was immediately returned to the respirator. The patient had a fair night following tracheotomy and on the following day, December 25th, 50,000 units of the botulinus antitoxin were again administered. Following injection of the antitoxin there appeared to be improvement in the general condition of the patient. He no longer had diplopia and he was able to breathe for a few minutes when outside the respirator.

On December 26th the patient again received 50,000 units of antitoxin and from then on a gradual general improvement was evident. The following day he was out of the respirator for a period of ten minutes and some increase in the strength of the muscles of the extremities was noted. By then he was able to swallow his salivary secretions. On succeeding days the patient tolerated longer periods outside the respirator and on January 3rd the tracheotomy was partially corked. He could tolerate closure of the cannula for only a few minutes upon the first attempts, but the periods of corking were gradually increased from day to day with the patient becoming less apprehensive of the procedure. On January 8th he was out of the respirator the entire day and the following day he was decan-

nulated. He was now able to take oral nourishment and muscle re-education was begun by the physiotherapist. He gradually regained much of his strength and was discharged from the hospital on February 2nd for home convalescence.

CONCLUSIONS

After reviewing numerous case histories in reported outbreaks of botulism and observing a case of botulism, it was noted that the problem of management is similar to that encountered in those cases of bulbar poliomyelitis having respiratory distress because of pharyngeal pooling of mucus. From the experience gained in the use of tracheotomy in selected cases in the Minneapolis poliomyelitis epidemic of 1946, we feel that tracheotomy may be a useful addition to the treatment of botulism.

SUMMARY

1. A brief résumé of the etiology, physiopathology, symptomatology and treatment of botulism is presented.
2. A case of botulism treated by tracheotomy in addition to the conventional methods of treatment is reported.
3. Tracheotomy should be considered in the program of therapy in botulism.

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XCIV

A CASE OF PEDUNCULATED CARCINOSARCOMA
OF THE HYPOPHARYNX

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The following case is of interest from a practical as well as from a pathological point of view. It shows large new growth occupying almost the entire hypopharyngeal spaces; but without any severe disturbances. The attachment of the tumor was determined only after operation. Moreover, the histopathological findings of the removed neoplasm show an interesting and rare picture: carcinosarcoma.

History and Findings. The patient, W. L., a male farmer, 28 years old, had for three months complained of a sensation of a lump in his throat or a slight dysphagia, but no pain or difficulty in drinking. He said that a sensation of tickling which excited him to cough was especially noticeable at night. Difficulty in breathing or phonating was never observed. Wheezing developed and was very marked after exercise. There was no hemoptysis or excessive sputum. On October 18, 1948, he entered our clinic where we noted the following findings and symptoms: He was weak and in poor physical condition. The face and skin were pale. Respiration was subdued and the voice reduced to a coarse whisper. Foetor oris was marked. Chest and abdomen showed no pathological signs. On admission the hemoglobin content was 95%. The blood count showed 4,790,000 red cells and 9,900 white, with polymorphonuclear leucocytes 72%, lymphocytes 23%, monocytes 5%. The erythrocyte sedimentation rate showed 28 (30'), 68 (60'), 97 (120'). Blood pressure was normal and the Wassermann reaction negative. Albuminuria or glycosuria was not found.

On pressing down the base of the tongue, one could see a globular growth rising from below leaning toward the left side behind the epiglottis. Characteristic and interesting was the laryngoscopic picture. The hypopharynx and the entrance to the larynx were closed by an egg-sized, elliptic, knobby and coarse tumor. The

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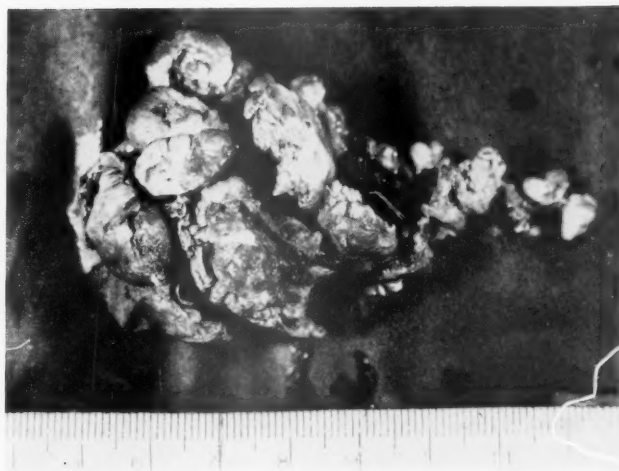


Fig. 1.—The hypopharyngeal tumor removed, after reconstruction.

overlying epithelium was reddish, blood-red, violet, or whitish where edema was present. The right portion of the tumor was smaller and between this and the main tumor mass on the left, necrotic changes existed. The right side of the epiglottis and right pyriform sinus were visible and free. Palpation with a probe revealed that the tumor had a firm, elastic consistency; and no place of adhesion with the hypopharyngeal wall or with the epiglottis could be found. The point of origin could not be located. The left side of the neck bulged slightly, but no glands or infiltration in this area could be palpated.

A biopsy specimen showed a few cell nests of adenocarcinoma embedded in a stroma rich in cells. The carcinoma cells in each nest were irregularly stratified, but of adenomatous structure. The nuclei of the cancer cells were large, round, ovoid or polymorphous, and with scanty chromatin. Mitotic figures were seen in varying number, though usually not numerous. Beneath the normal lining epithelium edematous changes and leucocytic infiltration were marked. In some areas, hemorrhages and capillary new formation were also striking.

Because of the laryngoscopic findings and in view of the microscopic picture, the neoplasm was thought to be most likely a malignant and bleeding one, so it was considered necessary to remove it by the external route.

Operation. Under local anesthesia a preliminary tracheotomy was performed, followed by laryngofissure. After the larynx was opened by dividing the thyroid cartilage at the median line, the smaller tumor was exposed in the upper part of the operative field of the larynx, but neither the subglottic spaces nor the vocal cords nor the false cords showed signs of tumor involvement. This smaller tumor was removed with the cold-wire snare.

At this stage neither the upper limit nor the originating site had yet been discovered. The lower portion of the tumor was seen to descend behind the left arytenoid and aryepiglottic fold. Subhyoid pharyngotomy was done as the next step. The top of the tumor was now exposed rising over the superior border of the epiglottis. The tumor was then removed in pieces (Fig. 1). The subhyoid mucous membrane opening was closed with catgut and the T-shaped skin opening sutured without much bleeding. Healing of the wound was satisfactory, so that the tracheotomy tube could be removed without dyspnea a week after the operation.

Endoscopic view on the thirteenth day after the operation showed that the left lateral posterior wall of the hypopharynx was slightly and diffusely elevated, but the overlying mucous membrane was smooth and clean. From below this area to the left pyriform sinus it was granulated, soft, and covered with grayish white coating. Here the attachment of the tumor had, with difficulty, been determined at last. The postcricoid region of the esophagus was freed. The right arytenoid was edematous, and the left arytenoid was mobile and acted like a valve during respiration. No other tumor could be found in the larynx.

Irradiation with radium was begun perorally on the eighteenth day after the operation. The left pyriform sinus became gradually deeper.

The patient was discharged from the hospital on the thirty-seventh day after the operation for family reasons.

The tumor sprang from the left lateral posterior hypopharyngeal wall and the left pyriform sinus subepithelially, with a short and slender peduncle. It then towered over the upper edge of the epiglottis. As a whole, it formed a longish cone. It measured about 6.0 cm long, 3.2 x 2.5 cm at the upper portion, and 0.5 x 0.8 cm at the pedicle. It weighed 14.9 gm. It was elastic, dense in consistency, and the cut surface appeared grayish, or milky white, and firm. In some places it was bloody.



Fig. 2.—Photomicrograph demonstrating an adenocarcinomatous area.

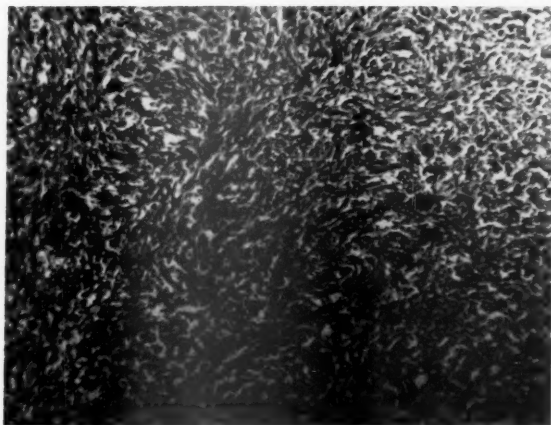


Fig. 3.—Photomicrograph demonstrating sarcomatous features.

Sections of the several portions were examined microscopically. The picture of adenocarcinoma now became more typical and clearer (Fig. 2). Of interest was the stroma which consisted in some areas of spindle shaped cells running in bundles or whorls with many delicate fibers which were reddish by van Gieson stain. In other places the cells were somewhat different; they were varied in size, spindle shaped or polygonal, and rich in protoplasm. Their nuclei were also oval, poor in chromatin and occasionally with nucleoli. Mitotic figures were seen, though not numerous. In these regions reticulum fibers were very abundant, as demonstrated by silver impregnation. According to these findings, we were dealing with sarcomatous tissue (Fig. 3). Moreover, there were places in which capillary hyperplasia was so excessive that it suggested the picture of so-called gemmangioma.

DISCUSSION

Neoplasms of the hypopharynx include both malignant and benign growths originating in the area lying between two planes, one passing horizontally through the inferior portion of the base of the tongue and the other passing parallel to the first, through the mouth of the esophagus. They thus have a close relation to both the larynx and the esophagus.

Disturbances caused by hypopharyngeal malignancy, especially by carcinoma, are generally so severe that the lesions are seldom overlooked. On the other hand, benign growths occurring in this area, which usually develop with a pedicle, are so slow in evolution that the symptoms associated with such pedunculated tumors are vague during the early stages. Some slight signs, such as discomfort or paresthesia in the throat, cough, or dryness of the throat are usually the only complaints. Occasionally, the tumors hide themselves in the neighboring hollows, and consequently the tumors are very difficult to discover. They are let alone, as a rule, until they have considerably enlarged. In this stage, partial blocking of the air or food passages gives rise to such signs as dyspnea, dysphagia, or odynphagia. The detection of these tumors may not be difficult, but revealing their origins is not always easy.

Giant hypopharyngeal tumors reported in the literature include those described by Georke (30 cm long), Garreston (15 cm), Minski (14 cm), Gorbel (13 cm), Nepreu (12 cm), Lennander (9 cm), Hatano,³ Tanabe (8 cm), Herbst (7 cm).

Owing to their vague symptoms and slow development, these tumors are generally reported in older persons. Most patients were

over 50 years of age, with the exception of the following reports: 27 years (Kenyon), 32 years (Goebel), 33 years (Cheval), 38 years (Gerber), 39 years (Herbst), 44 years (Hatano).

According to Trotter, tumors of the hypopharynx can originate from different parts of the hypopharynx, such as (1) aryepiglottic folds, (2) pyriform sinus, (3) lateral wall of the hypopharynx, (4) posterior wall of the hypopharynx, (5) postcricoid region. Among these forms, pyriform sinus growths are rarely seen during their early, small, localized stages of development. The location of these growths in the pyriform recess causes no difficulty that is detected on the part of the patient until the tumors have reached sufficient size to encroach upon the pharyngeal lumen and thus cause some local discomfort that may increase with their growth until actual dysphagia is produced. The posterior pharyngeal wall growths are also relatively rarely seen clinically.

Mikulicz and Huehnemann have stated that hypopharyngeal tumors most frequently arise from the pyriform sinus, epiglottis and aryepiglottic fold, but Goebel and Hatano suppose that posterior wall neoplasms are more frequent, though these growths may often escape notice. Pedunculated neoplasms originating in the hypopharynx are mainly found to be benign growths. Lipoma and fibroma, or mixed forms are more often reported in the literature; while papilloma, hemangioma and lymphangioma come next.

In regard to the pedicle formation of malignant tumors, only three descriptions have been given in the many reports of hypopharyngeal cancers. They are by Hopmann in 1910, Flecken in 1912, and Jes in 1926.

Among the rare hypopharyngeal sarcoma cases, Navratil, Cohn, and Brown described those developing from the pyriform sinus and lateral hypopharyngeal wall, and Koga⁴ in 1933 reported a case of pedunculated sarcoma originating from the lateral wall of the hypopharynx. In the reports of Lodder, Felix, Delmas, Cannier and Lange, the pedicles of the tumors were attached to the posterior wall of the "pharynx."

The problem of carcinosarcoma has been of interest since the time of Virchow. It has been a subject of much dispute, and there has been no agreement among pathologists and oncologists concerning the existence of such an entity. In the world literature about 200 cases of so-called carcinosarcoma have been reported. Though the nomenclature has been varied, it might be considered legitimate to call such a tumor "carcinosarcoma" or "sarcocarcinoma," when

both carcinoma and sarcoma are concurrently found. The term "carcinoma sarcomatodes" should be limited only to tumors in which a purely epithelial growth has a sarcomatous aspect.

In respect to its development, possibility of the "mutation tumor" is questionable, while confirmation of the "combination tumor" (the product of the growth of two different blastomatous portions derived from one stem cell) is very difficult in a mature tumor. In point of fact, both the "collision tumor" (in which two primarily independent tumors invade each other), and the "composition tumor" (in which both parenchyma and stroma have become blastomatous) make up the majority of those reported in the literature.

Recently Saphir and Vass⁸ stated, after having reviewed 153 cases of such tumors reported in the American, French, English, German and Italian literatures, that the majority of these so-called carcinosarcomas can be interpreted as carcinoma on the basis of morphologic cellular variation.

Pearlman⁹ also concluded from a study of the world literature of carcinosarcoma of the esophagus and his own cases that the existence of so-called carcinosarcoma in the esophagus as elsewhere was very questionable.

Frank and Lev¹⁰ also discarded this classification following their study of 62 cases of cancer and 5 cases of carcinosarcoma of the larynx. Almost half of the squamous and more than half of the transitional cell carcinomas showed a tendency towards sarcomatous arrangement and the five "carcinosarcomas" were not carcinosarcomas but variants of carcinomas.

In spite of these varying opinions, the existence of such an entity as carcinosarcoma is becoming recognized more widely.

Out of 153 carcinosarcoma cases quoted in Saphir and Vass' report, there were 14 cases occurring in the esophagus; 6 cases in the larynx; and one case each in the middle ear, maxilla, tongue, salivary gland and hypopharynx (Harvey and Hamilton). In Claessen and Mathias' report² of carcinosarcoma there was one each of the submaxillary gland, nose and pharynx (Hansemann). Also, Schwarz' publication,⁶ among five carcinosarcoma cases one case each of the tongue, vocal cord, and pars buccalis pharyngis was found.

As may be seen, the case reports of carcinosarcoma in the otolaryngological field are not so often encountered. Neither in the Chinese nor in the Japanese literature has such a case been reported.

In Formosa, Kawano⁵ in 1933 reported a case of carcinosarcoma of the stomach. Recently Lin and Chang¹¹ published a rare case of the eyelid with detailed review on the subject of carcinosarcoma.

Among 43 carcinosarcoma cases described in Claessen's papers, there were only two patients under 30 years of age.

Only two reports of hypopharyngeal carcinosarcoma have been given. They are by Kahler¹ (1908), and by Harvey and Hamilton (1935). The former occurred in the pyriform sinus and was of infiltrative form. We have been unable to see the detailed papers on the latter case.

SUMMARY

A case of carcinosarcoma of the hypopharynx is recorded.

The tumor was found to arise subepithelially with a narrow pedicle from the left pyriform sinus and the left lateral posterior wall of the hypopharynx. It may belong to the combined form of the growths originating from the pyriform sinus and the posterior wall of the hypopharynx according to Trotter's classification. The origin of the tumor, especially the attachment of the pedicle, was exactly determined on the thirteenth day after operation by means of endoscopy. Both laryngofissure and subhyoid pharyngotomy were performed. It was not possible to remove the tumor as a whole, but in pieces, since it was so large that the site of origin could not easily be discovered. The size of this tumor was considerably larger than those described in the literature referred to above.

Since the patient was only 28 years old, we may be reporting one of the earliest cases of large hypopharyngeal tumor or of carcinosarcoma.

The microscopical sections revealed adenocarcinoma and juvenile fibrosarcoma. Since the case had progressed only three months, the sarcomatous portion had not yet become typical. Summarizing the histopathological findings the tumor might be interpreted as a "composition tumor" in which the stroma of the primary adenocarcinoma showed up as secondary to the sarcomatous features.

Apparently such carcinosarcoma is rare in the otolaryngological field. Still rarer and more of interest was the fact that it arose from the hypopharynx with a narrow pedicle.

A discussion is given of the problem of carcinosarcoma with special relation to tumors of hypopharyngeal origin.

The author is deeply indebted to Prof. T. Lin, Prof. S. Yeh, and to Dr. W. Lin for their most valuable advice and assistance.

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THE INTRATEMPORAL REPAIR OF FACIAL PARALYSIS

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Intratemporal facial nerve repair is preferable to other means of treatment in cases of peripheral facial paralysis due to trauma or disease. Even though muscular movement returns after repair of a damaged or severed nerve the finer facial movements used in expressing the various emotional states may remain permanently lost. The frontalis muscle seldom functions after it has been paralyzed, and the damage probably is in the small branch of the facial nerve supplying the muscle rather than in the muscle itself.

The intratemporal surgical treatment consists of facial decompression, end to end anastomosis, nerve grafting, or anastomosis with other motor cranial nerves. In cases of Bell's palsy that do not recover spontaneously decompression of the nerve is indicated. End to end anastomosis or nerve grafting gives the best results in traumatic facial paralysis. In Case 3 herein reported, tantalum foil was used to cover the nerve graft, but function failed to return. Facial anastomosis with other cranial nerves is reserved for cases that have not improved after other surgical procedures or in those in which the central end of the facial nerve can not be located. Reconstructive facial surgery is necessary while awaiting return of nerve function, when too great a portion of the nerve has been destroyed to allow repair or when associated muscular atrophy is present.

CASE 1.—*Bell's Palsy with Recovery Following Decompression of the Facial Nerve.* While riding in an open car exposed to a cold wind a 34-year-old man complained of pain over the right mastoid region, and the following day he noticed drooping of the right side of the face. The pain about the ear slowly disappeared, but the palsy remained unchanged for the next three months. He stated that his mother had a facial paralysis, the cause of which was unknown.

Examination revealed a paralysis of the right facial nerve, peripheral type including the chorda tympani nerve, with no response

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Fig. 1.—Right facial paralysis, following injury to facial nerve during mastoidectomy.

to faradic or galvanic stimulation. There was no disease of the mastoid either clinically or by roentgen examination. At the end of three months a facial decompression was performed. The bone was removed along the facial canal from the middle ear to the stylo-mastoid foramen exposing an edematous and discolored facial nerve. The nerve sheath was injected with 1 cc normal saline solution, and the wound was closed without drainage.

Galvanic and faradic response returned respectively three and six weeks after operation. There was a gradual improvement in voluntary control of the face, the patient recovered complete movement of the face including the frontalis muscle, and taste returned over the anterior two-thirds of the right side of the tongue.

CASE 2.—Facial Paralysis with Recovery Following Nerve Graft. A 22-year-old man had a simple right mastoidectomy performed at another hospital for an acute suppurative otitis media and mastoiditis. After operation he developed a facial paralysis with spontaneous recovery in a week. The ear continued to drain, and the patient had two severe attacks of pain and high fever. Roentgen films of the mastoid revealed a large number of remaining cells with cloudiness.

Two months after the original operation the patient was advised to have secondary mastoidectomy. At operation only a small



Fig. 2.—Beginning recovery of right facial paralysis following nerve graft. This patient regained all facial movements except the forehead.

filament of the facial nerve remained from the horizontal semicircular canal downward for approximately 6 mm. During the operation this filament of nerve was injured further and was immediately repaired by a nerve graft (Fig. 1).

A 6-mm segment of the anterior femoral cutaneous nerve was placed between the ends of the nerve and silver foil laid over the graft. After a small rubber drain was placed in the wound light packing was used. One week later a secondary plastic closure was performed, and when the graft was inspected it was accurately located between the ends of the facial nerve. Six months after operation function began to return to the face, and recovery became complete except for the frontalis muscle (Fig. 2).

CASE 3.—Facial Paralysis with Failure of Nerve Graft, Following Use of Tantalum Foil. Immediately following mastoidectomy at another hospital for an acute suppurative otitis media, a 20-year-old man developed complete right sided facial paralysis with chorda tympani involvement. Facial injury was not recognized at the time of operation. One month later upon opening the mastoid cavity the proximal end of the facial nerve was located beneath the horizontal semicircular canal while the distal segment was found at the level of the chorda tympani nerve. After unroofing and freeing the nerve from its canal bed the nerve ends were cut cleanly with a

scalpel. Three segments of the anterior femoral cutaneous nerve were placed in the gap forming a cable bridge between the divided ends of the nerve. Gum acacia glue was painted over the ends of the graft, and a strip of tantalum foil was placed over the facial canal to prevent dislodgment of the graft. Following operation there was intermittent discharge of pus from the ear, and the tantalum foil was visible through an opening in the posterior canal wall. Fibrosis occurred around the visible tantalum foil, and facial function failed to return after eight months. The patient refused further operation for removal of the tantalum with either direct nerve anastomosis or regrafting.

CASE 4.—*Facial Paralysis with Anastomosis to the Spinal Accessory Nerve.* A complete left sided facial paralysis occurred in a 33-year-old man following mastoidectomy for chronic suppurative otitis media. Injury to the facial nerve was not recognized by the operator until complete facial paralysis developed immediately following operation. The patient consulted me four months later and consented to exploration of the facial nerve.

Upon isolating the distal end of the severed nerve in the mastoid cavity near the horizontal semicircular canal a neuroma was found. Search of the middle ear up to the geniculate ganglion failed to disclose the proximal end of the nerve. The distal segment was removed from its bony canal, the neuroma was excised and anastomosis with the spinal accessory nerve was accomplished with three .003 tantalum wire sutures.

Three months after operation facial muscular movement with the exception of the frontalis reappeared accompanied by associated movement, to which the patient adjusted satisfactorily.

The Scientific Papers of the American Broncho-Esophagological Association

XCVI

THE EARLY DIAGNOSIS OF BRONCHOGENIC CARCINOMA

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Bronchogenic carcinoma not so long ago was considered a relatively rare disease. In the past few years, however, the increasing number of cases and the importance of making an early diagnosis have received a great deal of attention.

Carcinoma of the lung, as shown by statistics, is definitely becoming more common, so any contribution to its early diagnosis should be of interest to the entire medical profession.

In the period between 1852 and 1876, Reinhard¹ was able to find only five cases of primary carcinoma of the lung in 8,716 autopsies (0.05%). Fuchs² in Munich could find only eight cases in 12,307 autopsies (0.06%). In the years between 1925 and 1931, of 7,855 autopsies received from the Pathological Institute of the German University of Prague³ 80 bronchial lung cancers were found, comprising 1.02% of all cases received. Johnson and Reinhart⁴ found the incidence of pulmonary carcinoma at autopsy had increased from 0.54% in the number of cases from 1932 to 1937 to 0.92% of autopsies performed in the period between 1937 and 1942.

At the present time carcinoma of the bronchus in males is second only to carcinoma of the stomach and the incidence is increasing. It is fatal to 15,000 people each year. There is no definite explana-

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

tion as to the cause of so many more cases in the past few years. Some have attributed tuberculosis and syphilis as an etiologic factor, but these apparently have not been found to have any relationship to the condition. Smoking often has been considered as a cause of malignancy in the lower respiratory tract, but women now smoke almost as much as men and there has been little increase in cancer of this type in females.

A more recent theory is that the inhalation of radio-active dust has some etiologic bearing on this type of disease. This is given some support because in an investigation of workers in the cobalt mines of the Schneeberg district of Saxony, Germany, and also in laborers in the uranium mines of Joachimsthal in the Sudetenland, a high incidence of carcinoma of the lung was found. It has been estimated that in Joachimsthal 50% and over of all workers were affected. At Schneeberg 75% of the miners had some involvement.⁵

Carcinoma of the lung is more frequent in males than in females. The relationship has been found to be approximately four to one, and here it is much higher. Ochsner and De Bakey⁶ in a collection of cases of 6,769 males, reported the rate to be 78.9%, whereas in 1,806 females it was 21.1%.

NO. OF CASES		%
Males	27	93.4
Females	2	6.6

AGE GROUPS	NO. OF CASES
21-30	1
31-40	1
41-50	3
51-60	11
61-70	13
71-80	0

It is more prevalent between the ages of 50 and 70, although one case has been reported in a child ten months old.¹⁴ The right lung is involved more frequently than the left. About 90% of cases are found in the hilar region.

In the 29 cases in this series there were 27, or 93.4%, males, and two, or 6.6%, females. The ages varied from 29 to 68 years of age, the highest incidence being between the 60- and 70-year group.

Pathology. About 90% of lung malignancies are bronchogenic in origin and are of the carcinomatous variety. Sarcoma and tumors of the pleura are extremely rare. Over 80% of bronchogenic carcinomas occur in the main bronchus and are thus accessible to bronchoscopy.

There are three types of bronchial malignancies which are recognized microscopically:

1. *Squamous cell.* This is the most common type. It usually is found in the main bronchus and secondary subdivisions close to the hilus, grows slowly, and metastasizes later than other types. It is best suited for surgical resection and constitutes about 50% of bronchogenic malignancies.

2. *Undifferentiated or the anaplastic variety.* This is the most malignant type. It occurs most frequently in the main stem bronchus, spreads rapidly, and metastasizes early. It is practically always fatal and makes up about 20% of bronchial malignancies.

3. *Adenocarcinoma.* This occurs in the finer bronchial divisions, usually near the periphery. It has a tendency to early metastasis and comprises approximately 30% of bronchogenic malignancies.

The squamous cell variety remains localized for a fairly long period of time and tends to produce ulceration or stenosis of the bronchus. These grow out into the lumen of the bronchus, producing obstruction and atelectasis, or often have a ball valve effect and produce emphysema. Other types may extend submucosally, destroy bronchial cartilages, and infiltrate the surrounding lung parenchyma. The undifferentiated type and the adenocarcinoma are fast growing and are apt to replace an entire lobe of the lung with malignant tissue.

Carcinoma of the trachea is uncommon and little can be done for it. Likewise, bronchogenic carcinoma which has extended up to the carina offers a poor prognosis.

Metastasis from lung cancer is varied and can invade any organ in the body. The route follows the rich lymphatic supply surrounding the lung. The pretracheal and mediastinal nodes are usually the first sites of metastasis. Bronchogenic carcinoma is the most common cause of metastatic cerebral lesions.

A series of 3,047 cases was collected by Ochsner.¹¹⁻¹³ The following is a list of metastatic sites and the frequency of occurrence:

SITES OF METASTASIS	FREQUENCY
Lymph node	72.2%
Liver	33.3%
Pleura	29.8%
Other lung	23.3%
Osseous structure	21.3%
Adrenal gland	20.3%
Kidneys	17.5%
Brain	16.5%
Heart and pericardium	12.7%
Skin	3.6%

Symptoms. The symptoms of lung cancer are varied and depend largely upon the location and cellular characteristics of the tumor. The squamous cell variety produces an insidious set of symptoms, whereas the undifferentiated type usually produces a fatal condition. For the benefit of the patient the recognition of early symptoms may mean the difference between life and death. A diagnosis made after metastasis is only of benefit from a didactic point of view and is of little value to the patient.

The most common symptom is that of a cough resulting from bronchial irritation. A cough can be productive or nonproductive, depending on whether a suppurative process such as an abscess or bronchiectasis is present. Hemoptysis of varying degree is another frequent symptom and in the absence of tuberculosis should make one highly suspicious of cancer. It may be present as blood-tinged sputum or as frank hemorrhage. Hemoptysis may be either an early or a late symptom. It is interesting to note that in a majority of cases low-grade fever is present and in this series was found in 62%. Chest pain, although a common symptom is not an early one and usually indicates peripheral or pleural extension. Weight loss is a symptom always present in advanced cases and to a milder degree in earlier cases. Various gastro-intestinal symptoms may be present, such as anorexia, eructation, bloating, nausea, and vomiting. These may probably be explained as a vagus reflex caused by irritation of the bronchus or by toxic effects.

Wheezing is a fairly common symptom, usually unilateral, and is attributed to partial obstruction of the bronchus. Unilateral wheezing at any age should be investigated thoroughly and should include a bronchoscopic examination.

Almost uniformly present in one of the stages of bronchogenic carcinoma is dyspnea, the severity of which depends upon how much lung tissue is involved. Since atelectasis is a result of bronchial obstruction, the more complete the obstruction the more extensive is the atelectasis, and, hence, the greater the dyspnea. Unexplained dyspnea in a person over 40 should warrant a roentgenogram and possibly a bronchoscopic examination.

SYMPTOMS	NO. OF CASES	%
Cough	24	82.1
Weight loss	23	79.3
Fever	18	62.1
Dyspnea	17	58.6
Hemoptysis	16	55.1
Chest pain	15	51.7
Gastro-intestinal symptoms	14	48.2
Wheezing	3	10.3

Pleural effusion, hoarseness, Horner's syndrome, and various other neurologic signs are always late symptoms and indicate extensive involvement and metastasis.

It is interesting to note that approximately 12% of the patients who die of carcinoma of the bronchus do not have any symptoms referable to the chest.

The duration of symptoms is anywhere from four weeks to 36 months, the average being about six to ten months.

In this series the shortest duration was found to be six weeks, whereas the longest period was 20 years or more. It is doubtful whether this one patient had carcinoma for 20 years, but he claimed that the character of his cough had not changed in that period of time.

Cough was found to be the most common and persistent symptom (82%), with weight loss running a close second (79%). Uniformly, all the patients complained of some weakness or lassitude.

Above is a chart showing the percentage and occurrence of symptoms in the 29 cases reported.

Diagnosis. In the days before improved roentgenographic technique, bronchoscopy and thoracic surgery, lung cancer was only diagnosed at the autopsy table. Even after bronchoscopic technique improved and the diagnosis of cancer was made before death in a small number of cases, the treatment was meager and these patients always died. It was not until Graham in 1933 performed the first successful pneumonectomy for carcinoma of the lung that the previously condemned patient had a chance for survival. The thoracic surgeon could do something for the patient if the condition was revealed early enough. The responsibility of making an early diagnosis lies primarily with the physician who first sees the patient with various and sometimes obscure complaints. Responsibility does not rest entirely with one physician but depends upon the co-operation and teamwork of several physicians. The internist, roentgenologist, bronchoscopist and thoracic surgeon are equally responsible for making an early diagnosis. There are a few cases where the symptom complex is so obscure that making an early antemortem diagnosis is impossible; however, it is imperative that every diagnostic procedure in the armamentarium be used. Any obscure chest complaint must be considered a bronchogenic carcinoma until proven otherwise. At times cancer of the lung occurs simultaneously with some pre-existing pathologic condition such as lung abscess or bronchiectasis, but more often these conditions are secondary to a lung malignancy.

Roentgenology. Secondary only to bronchoscopy the roentgenogram is an invaluable aid in diagnosing lung cancer. In the majority of cases there is definite roentgenographic evidence suggesting bronchogenic carcinoma. The usual findings are a hilar mass, atelectasis of a lobe or a suppurative process distal to an obstructing growth. Advanced cases will show mediastinal and tracheal shift, pleural effusion, or hydrothorax. Some difficulty will be met when the findings suggest an acid-fast lesion, lung abscess or bronchiectasis. Oftentimes a diagnosis of unresolved pneumonia or pneumonitis is made and valuable time is lost before the physician recognizes the fact that the patient's condition is much worse than the roentgenographic findings indicate.

Frequently the roentgenogram shows an obstructive emphysema which is indicative of a ball valve type of bronchial obstruction. This type of lesion is usually discovered early and can best be made by taking roentgenograms during inspirations and expirations.

Bronchography is helpful in demonstrating bronchial obstruction, especially in the second bronchi. It also reveals any underlying bronchiectasis or lung abscess.

Roentgenologic evidence of varying degrees was present in this series. The lesions varied from a mild lobular infiltration to massive atelectasis and hydrothorax. In not one single instance was the roentgenogram negative; the majority of cases showed atelectasis or infiltration involving one or more lobes.

The following chart shows the distribution of roentgenologic findings:

ROENTGENOLOGIC FINDINGS	NO. OF CASES	%
Atelectasis, massive or segmental	7	24.2
Infiltration or mass in lobe	12	41.4
Hilar mass	4	13.8
Suppurative lesions	1	3.3
Effusion	5	17.3

Bronchoscopy. Without a doubt bronchoscopy is the most important single procedure in the diagnosis of carcinoma of the lung, since approximately 80% of the cases can be diagnosed by this means. The findings depend upon the location and size of the lesion. Any ulcerations, growths or stenosis of the bronchus should have a careful biopsy of the surrounding tissue. Sometimes the only indication of bronchogenic carcinoma involving the secondary bronchi is a fixation with compression of the segments. A profuse purulent discharge accompanied by congestion and injection of the bronchus indicates a secondary suppurative process usually distal to the malignancy. Compression of the main bronchus, tracheal shift, and thickening of the carina indicate extensive involvement and an unfavorable prognosis.

Clarf and Herbut^{20, 21} reported a series of cases in which by staining and inspection of bronchial secretions they could make a diagnosis of carcinoma in 82.4% of the cases compared to 68.4% discovered by biopsy. They further found that in 21% of the cases there was no bronchoscopic evidence of malignancy, but the examination of secretions revealed malignant cells. Secretions are collected routinely at bronchoscopy, smeared and fixed in equal parts of 95% alcohol and ether and stained by the method of Papanicolaou. It is important that the secretions be smeared and fixed immediately so that the cells will not undergo autolysis.

The bronchoscope has its limitations. It cannot penetrate corners up into the upper lobe orifices, nor can it reach far enough into the secondary divisions.

Bronchial secretions are more reliable than sputum, because the sputum is usually highly diluted and mixed with various epithelial cells of the oropharynx. Although in Europe up to 86% of the cases are reported as showing sputum positive for malignant cells, that success has not been equalled at this clinic. The cases in which the sputum was positive for malignant cells usually had positive biopsy or cytologic evidence of malignancy in the bronchial secretions. As a rule these cases were far advanced and the diagnosis was of little help to the patient.

It has been the practice here to culture routinely the bronchial secretions for tuberculosis, predominating organisms, and for fungus. Likewise, smears are made for Papanicolaou stains and the rest of the secretions are sent to the pathology department for examination of the sediment. Occasionally a small piece of malignant tissue is found in the sediment, although the bronchoscopic examination is negative. Even when the bronchoscopic findings are characteristic and it is evident that the biopsy specimen will show malignant tissue, all the bronchial secretions are saved for cytologic studies.

The cases selected in the series have been proven microscopically to be bronchogenic carcinoma. The diagnosis was made either by biopsy and examination of the secretions through the bronchoscope, or by exploratory thoracotomy and biopsy of the malignant tissue or mediastinal nodes.

These cases were collected from 1946 to October, 1948. The Papanicolaou technique had been in use for approximately eight months.

The figures are not as good as those reported by Clerf and Herbut but the success attained in these cases has been most encouraging. A positive diagnosis of carcinoma was made in nineteen or 65.5% of the cases by bronchoscopy.

In breaking down these cases seven successful biopsies or 24% were made and the cytologic studies of bronchial secretions produced positive diagnosis in eleven cases or 55%. Five cases showed the sediment of the bronchial secretions to contain malignant tissue for a 28% average. One case that revealed cytologic evidence for malignancy also had a positive biopsy, and one case showed malignant cells to be present in the sediment.

It is interesting to note that, contrary to other reports, this series revealed the squamous cell variety in 14 cases and the anaplastic type to be the same number or an average of 48% for both. Only one adenocarcinoma was found in this series.

In 26 of 28 patients bronchoscoped, a tentative impression of carcinoma of the lung was made. Only one case was found to be negative and one was reported as chronic bronchitis.

CHART OF 29 CASES WITH A POSITIVE DIAGNOSIS

METHOD OF ESTABLISHING DIAGNOSIS	NO.	%
Bronchoscopy	19	65.5
Biopsy	7	24.1
Cytologic smears	11	55.0
Sediment	5	27.7
Exploratory thoracotomy	9	31.0
Pleural fluid	1	3.4
TYPE OF MALIGNANCY FOUND		
Squamous cell	14	48.2
Undifferential	14	48.2
Adenocarcinoma	1	3.1
RESULTS OF BRONCHOSCOPIC EXAMINATION		
Mass in bronchus	9	
Stenosis and fixation of bronchus	16	
Bronchiectasis	1	
Negative examination	2	
Not bronchoscoped	1	

Another diagnostic procedure sometimes used is aspiration biopsy. This is mentioned only to be condemned as a blind, inaccurate procedure. Its dangers are far in excess of its value, and it has no place among modern procedures.

Extremely important in making an early diagnosis of bronchial cancer is recognition of the fact that a patient may have a carcinoma and still have negative or minimal roentgenologic and bronchoscopic

findings. In patients between 50 and 70 years of age, even when bronchoscopic and roentgenologic evidence is lacking an exploratory thoracotomy should be done. At present with improved surgical and anesthesiologic techniques exploratory thoracotomy carries a low mortality rate.

Fortunately, in the majority of cases the roentgenogram and bronchoscopic examination will give some indication of a bronchial malignancy, its location and extent. It is the early bronchogenic carcinoma which must be diagnosed if the patient is to be saved. Physicians should be able to recognize early symptoms and must be "bronchogenic carcinoma conscious" if an early diagnosis is to be made. It is the consensus of opinion at the present time to consider cancer as a nonurgent condition. This is an erroneous view and a dangerous one for the patient. Any patient in whom cancer is suspected should be an urgent case, just as in the case of acute appendicitis. The high mortality of perforated appendices in the past was attributable either to a delay in operation or a delay in diagnosis. The same is true in primary carcinoma of the lung. The short period of two or three days may make the difference between a localized resectable lesion or one in which a few small cells have diffused into the lymphatic vessel and spread to regional nodes or other organs. Carcinoma must be attacked before it metastasizes if there is to be a cure for it. Bronchoscopy and exploratory thoracotomy seem to be radical diagnostic procedures, and that is true. However, if being radical enables one to make an early diagnosis of bronchogenic carcinoma, it is advisable to be radical and have a live patient rather than to be conservative and wait to make the diagnosis at the autopsy.

CONCLUSIONS

1. Bronchogenic carcinoma is on the increase both relatively and absolutely.
2. Any surgical procedure done must be undertaken early, before metastasis occurs.
3. Typical symptoms are cough, hemoptysis, wheezing, chest pain, fever, weight loss, or signs of lung suppuration.
4. The authors have been successful in using Clerf and Herbut's technique in examining bronchial secretions for malignant cells. Diagnosis by cytologic study was made in 55% of the cases and by biopsy in 24%. In this series a positive diagnosis was made by bronchoscopy in 65% of the cases.
5. Even though bronchoscopy and roentgenologic evidence are lacking, if a carcinoma of the bronchus is suspected an exploratory thoracotomy should be done.

6. Cancer of any type should be considered an emergency. A delay in making an early diagnosis is just as serious as failing to diagnose acute appendicitis in the early stage.

104 WEST MADISON STREET.

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XCVII

REPORT OF A CASE OF FIBROLIPOMA OF RIGHT MAIN BRONCHUS; BRONCHOSCOPIC REMOVAL

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PHILADELPHIA, PA.

A review of the literature reveals the incidence of fibrolipoma of the bronchi to be rather infrequent. Rokitansky¹ first called attention to the occurrence of a bronchial tumor in 1854. Feller,² however, was the first to clearly describe a case of fibrolipoma of the bronchus which he found postmortem originating in the right middle lobe region. Kernan³ reported three unusual cases of bronchial tumors in 1927, and one of these cases as a fibrolipoma originating at the bifurcation of the trachea.

In 1928 Myerson⁴ reported another case of fibrolipoma originating from the left upper lobe bronchus, which he was able to successfully remove bronchoscopically. In his paper he called attention to the fact that only 26 cases of benign tumors had been reported in the literature to that time, and fibrolipoma was the most infrequent.

It was also of interest to note that of these 26 cases of bronchial tumors 11 were not only recognized on bronchoscopic examination but also removed bronchoscopically. The other 15 cases were found at autopsy, as reported by Reissner⁵ in a comprehensive review of the literature. Wessler and Rabin⁶ in 1932 reported 17 cases of benign tumors of the bronchi, in which was included a case of fibrolipoma originating from the left lower lobe bronchus. In the same year Jackson and Jackson⁷ reported a series of cases of inflammatory tumors of the bronchi, of which two cases were suggestive of fibrolipoma.

In 1934 Honig⁸ discovered a case postmortem in a man 54 years of age. The following year Morlock and Pinchin⁹ reported in detail the records of nine cases of benign neoplasms. In 1938 Pollock, Cohen and Gnassi¹⁰ reported one case of fibrolipoma in 104 cases of benign bronchial growths. McGlade¹¹ reported his most interesting case the subsequent year

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

No other case could be found in the literature until the report of Vinson and Pembleton¹² in 1942. A recent report is the unusual case of endobronchial lipoma of the left upper lobe bronchus found at operation and presented by Watts, Claggett and McDonald.¹³ Whalen¹⁴ in 1947 reported the last case to be found in the literature.

To this series is added a case of fibrolipoma which I recently found and removed bronchoscopically from the right middle and lower lobe bronchus.

REPORT OF A CASE

J. J. K., a 40-year-old white male, an executive, was first seen on October 20, 1948. He gave a history of having had a cough for about two years, which he attributed to smoking. For the same length of time he had been aware of a purring-like wheeze in the right side of his chest. This he believed to be due to some mild allergy. Since he never suffered any severe discomfort no physician was consulted. He had noticed, however, that recently the wheezing noise in his chest had become more pronounced and that he would get short of breath on the slightest exertion. About four weeks previous to examination he had had a "virus infection" with fever and was confined to his home for about ten days. About seven days ago he had a sudden onset of severe pain in the right lower chest, with severe shortness of breath. He consulted his physician and was confined to his home for several days until his symptoms improved, and then was referred to a radiologist for films of the chest. X-ray studies made by Dr. Carl F. Koenig revealed the following findings:

"Fluoroscopically one at once notes the elevation and partial fixation of the right diaphragmatic dome with the heart pulled to the same side, with increased density towards the hilar area, suggesting atelectasis of the middle right lobe; this is noted when turning laterally to be the right middle lobe which presents marked increased mottled density, while the lower right lobe aerates posteriorly. This has been caused by a sudden bronchial block, whether or not a plug of thick, inspissated mucus or possible bronchial growth remains to be seen. The rest of the right lung field and left lung field is otherwise clear. Postero-anterior and lateral views show this atelectasis in the right middle lobe and I believe this man should be seen by a bronchoscopist. There is no history of blood-spitting, but an asthmatic history, and no history of any foreign body." (See Fig. 1.)

Because of the x-ray findings I was asked to see this patient in consultation and he was admitted to the Pennsylvania Hospital on October 22, 1948.

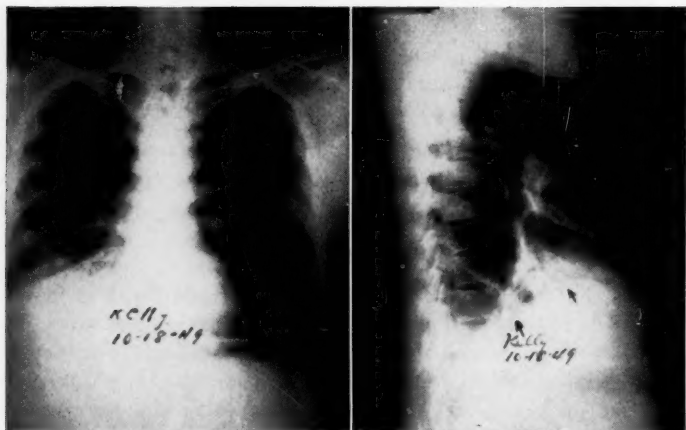


Fig. 1.

Physical examination on admission revealed the temperature to be 98.2° F., pulse 92, respiration 20, blood pressure 130/86. The patient at this time did not appear to be in any discomfort. He was not dyspneic. The positive findings were localized entirely to the right chest. On auscultation there was a definite wheeze audible over the region of the right main bronchus. This wheeze could also be heard distinctly as a purring sound if the patient breathed with his mouth open. The left chest was entirely negative.

Laboratory studies revealed erythrocytes, 4,900,000; leucocytes, 7,600 with 80% polymorphonuclear leucocytes and 20% lymphocytes, blood sugar 87 mg%, blood urea 11 mg%, Wassermann and Kahn tests negative, and urinalysis negative.

Bronchoscopic examination on October 22, 1948 revealed most unusual findings. "The motility of the larynx was normal; the mucous membrane was just mildly inflamed. The trachea was of normal caliber. The bifurcation was not thickened. The first portion of the right main bronchus revealed a normal lumen. However, at the lower half the lumen was completely obstructed by an irregular, grape-like growth, which filled the lumen completely. This tissue was not friable but very firm and resistant on several attempts at biopsy. However, several small pieces of this tissue were obtained and sent to the laboratory for histological examination. There is a possibility that this may be a benign mucosal new growth,

but I am more suspicious of a malignant process, particularly sarcoma. It certainly did not appear to be consistent with an adenoma. The recent episode of pain and marked dyspnea unquestionably was associated with sudden obstruction of the airway to the right lower and middle lobe, causing the massive atelectasis, and giving the patient the discomfort which he had. We should get added information from the material submitted to the laboratory for histological examination, which should give us some idea as to what the next step should be."

On histological examination the tissue removed on October 22, 1948 was reported as fibrous tissue. The cytological examination of the bloody material submitted for tumor cell study was reported negative for tumor cells.

Bronchoscopic examination was repeated on October 25, 1948. At this time a No. 8 full lumen bronchoscope was used and better visualization of the tumor mass was possible.

"We were again able to visualize the grape-like pedunculated mass which filled the entire lumen of the lower portion of the right main bronchus, occluding the openings leading to the middle and lower lobes. In attempting to obtain tissue for further biopsy I was successful in grasping the pedicle and almost two-thirds of the tumor mass was removed. The removal of this tissue reopened the bronchus and a profuse amount of thick, purulent material was then aspirated from the right lower lobe. The middle lobe orifice could then be visualized, but there still was some of this same type of tissue around the lumen. The tissue removed appeared like a pedunculated mass, and I am hoping that this is benign. If so this patient's problem is pretty well solved, and he should not have any further trouble, except that he should be watched closely for recurrence of the tumor mass. If the tissue proves malignant, however, surgical intervention is essential."

The following is the microscopic report of the tissue removed October 25, 1948: "Section shows that the bulk of the specimen is composed of large, clear, adult fat cells. In some areas there are moderate amounts of fairly dense fibrous tissue. In some places the free border of the latter is covered by a layer of transitional epithelium. Some portions of the specimen are heavily infiltrated by red blood cells. Some portions appear to be undergoing necrosis as evidenced by infiltration with neutrocytes and partial loss of cellular detail. In addition, the fibrous component contains occasional small to moderate sized collections of lymphocytes. In some parts of the adipose tissue there are small clusters of tubular glands lined by a single layer of cuboidal or low columnar cells. These cells have clear

cytoplasm and basally situated, round nuclei. Some of these mucous glands and their ducts resemble sweat glands, but they are interpreted as representing tracheal glands with metaplasia. No evidence of malignant change is seen. Diagnosis: Lipoma." (See Fig. 2 and 3.)

The patient was again bronchoscoped on October 29, 1948, with the following findings:

"Considerable more of the same type of fatty-like tissue was removed from the right main bronchus, particularly around the middle lobe orifice. After the removal of this tissue we were able to see the opening to the middle lobe and a large quantity of purulent material was aspirated from beyond it. The patient is being discharged from the hospital at present. However, he will need further recheck both by x-ray and bronchoscopic examinations."

Histological examination of the tissue removed on October 29, 1948, was reported as follows:

"Section shows that the specimen consists principally of adipose tissue. Scattered through this are irregular fibrous trabeculae of varying width. A few small clusters of mucous glands are also present. Some portions of the adipose tissue are partially bound by a zone of epithelium, the cells of which are arranged several layers in thickness. These cells are oval or elongated with oval vesicular nuclei and are characteristic of respiratory epithelium. Some portions of the adipose tissue are invaded by fibroblasts which are accompanied by a few multinucleated giant cells of the foreign body type. These changes presumably represent a response to surgical intervention on previous occasions. Evidence of malignant change is not found. Diagnosis: Lipoma."

The patient was discharged from the hospital on October 31, 1948.

An x-ray examination of the chest was made on November 26, 1948, after the third bronchoscopic removal of the tissue, and the following is the report of the x-ray findings:

"Re-examination of this patient since bronchoscopic removal of the intrabronchial lipomatous growth from the right middle lobe bronchus now shows that the right middle lobe has become fairly well aerated. The right dome of the diaphragm is smooth and moves quite well. The heart shadow is back in normal position and the rest of the lung field is aerating quite well. Increased pulmonary markings are at the right hilum down and out toward the middle lobe. After giving him barium to swallow films show the esophagus to be in the normal position. Films were made both in inspiration and expiration phases. The right middle lobe is now fully expanded

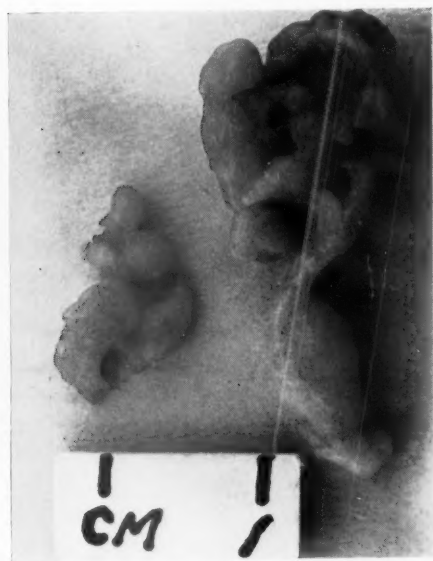


Fig. 2.

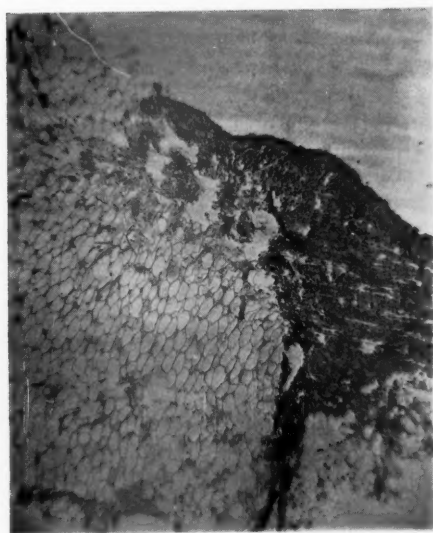


Fig. 3.

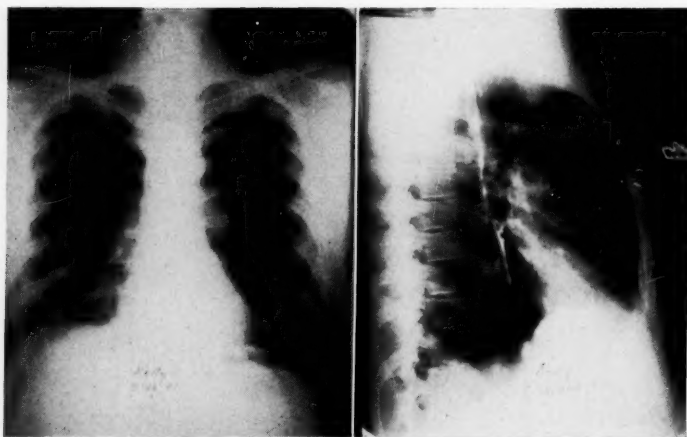


Fig. 4.

but showing increased pulmonary markings, no doubt residual to the bronchial blocking. No obstructive emphysema is noted to indicate any partial blocking at this time. The rest of the lung field is aerated quite well and considered normal. Laterally one sees a slight tenting effect at the right diaphragmatic dome which seems a little high. This is at the lower fissure between the right middle and lower lobe. Of course, the thing is to keep checking this patient's chest as this finding of lipoma is rather unusual but very fortunate." (See Fig. 4.)

He was readmitted to the Pennsylvania Hospital on December 3, 1948, for further bronchoscopic evaluation. Bronchoscopic examination was made on December 3, 1948, with the following findings:

"I was very pleased with the bronchoscopic findings today. The lumen of the lower lobe bronchus was completely open, allowing free normal aeration of the lower lobe. The middle lobe revealed only a small piece of residual tissue on the brim of the opening and this was removed today. The orifice of the middle lobe bronchus was otherwise completely patent and the patient should have normal aeration into this lobe also. I feel that this man is a very fortunate individual in the fact that the tissue which was present was lipomatous in nature rather than malignant. As far as we know this type of tissue does not have the tendency to recur very rapidly, but

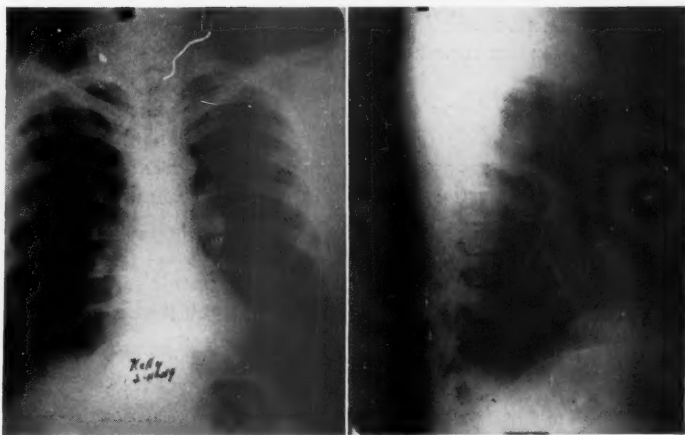


Fig. 5.

the patient should be kept under further observation and seen from time to time to make sure that there is no recurrence."

The histological examination revealed fibrous tissue.

He was discharged from the hospital December 4, 1948.

The patient was readmitted to Pennsylvania Hospital on February 11, 1949, for further bronchoscopic examination. X-ray studies made on February 11, 1949, were reported by Dr. Paul Bishop as follows:

"The examination of the lungs is now entirely negative. The shadow caused by the atelectasis of the right middle lobe revealed in our examination of October has entirely disappeared; the lung is well expanded and appears perfectly normal." (See Fig. 5.)

The bronchoscopic examination on February 11, 1949, revealed "practically no abnormality in the right main bronchus. The only variation from normal was the slight thickening of the septum between the middle and lower lobe openings. The middle lobe orifice was of normal caliber and the right lower lobe subdivisions were all of normal size. No abnormal tissue was present within the lumen of the bronchus at all at this time. I think that these findings are certainly gratifying and the prognosis here seems very good."

This patient was rechecked by x-ray examination on April 13, 1949, and the report was as follows:

"Re-examination of chest shows that the right lung field now aerates quite satisfactorily, as does the left lung field. Both domes of the diaphragmatic apparatus are working quite well and the tenting previously seen in the lateral view has disappeared. The esophagus shows no defect nor any displacement. The heart and mediastinal shadows show no displacement. The only thing noted was that he still has some increased pulmonary markings extending downward and outward at the lower right hilum. Laterally the middle lobe shows good aeration and one can make out the fissures. No evidence of any recurrent block is found and since his right lobes aerate quite well there are evidently patulous openings since the removal of the lipomatous growth from the right middle lobe bronchus. He looks quite well and feels exceedingly well. One would say this is a fairly normal chest now."

DISCUSSION

A review of the literature reveals that bronchial tumors in general are not very common and fibrolipoma is one of the most infrequent types of these inflammatory bronchial tumors. There has been considerable discussion as to etiological factors stimulating this type of growth and the basic structures from which it arises. Watts, Claggett and McDonald, in their recent investigation, have clearly demonstrated the presence of lipid cells in the submucosal region of the bronchi, and it could be assumed that any disturbance in the normal cell growth of these structures could readily produce the tumefaction. A careful résumé of the history of the individual cases reported in the literature is rather convincing that fibrolipoma is a very slow growing type of tumor.

Most of the patients have had a long duration of symptoms directly referable to this specific condition, ranging from periods of two to five years. Likewise the descriptions of the cases reported in the literature reveal that fibrolipoma is not an invasive tumor but rather of the pedunculated type which readily adapts itself to the contour of the surrounding confining structures. Thus the eventual occlusion of the involved bronchus is insidiously slow but sure. It is this same slow progression that may deceive the patient into a false security of well being in the early stages, particularly so since the wheeze which may be associated with the beginning bronchial obstruction could be readily dismissed as being caused by smoking or some minor unknown allergy. By the time the true condition is discovered irreparable damage may have been inflicted upon the portion of the lung beyond the point of obstruction because of the inadequate drainage and aeration. Consequently most of the patients

have a residual bronchiectasis of varying degree, dependent upon the extent of obstruction of the involved bronchus by the tumor mass.

To avoid these complications it is extremely important that any suspicion of pulmonary disease should be thoroughly investigated by all the aids at our disposal. One of the most important of these aids is the direct inspection of the tracheobronchial tree by bronchoscopy. Bronchoscopic examination performed by a well trained and competent individual will eliminate any doubt as to the presence or absence of endobronchial pathology.

SUMMARY

A case of lipoma of the right main bronchus originating at the level of the middle lobe orifice and obstructing both the middle and lower lobe bronchi, is reported.

From the history this growth was at least of two years' duration and possibly longer. The slow growth of this type of tumor did not produce any sudden onset of bronchial obstruction. Although the patient had been aware of the peculiar type of breathing which he described as a "purring noise" in his right chest, he had never consulted a physician for advice.

The complete obstruction of the right main bronchus precipitated symptoms of severe distress to require thorough investigation of his pulmonary difficulty. This not only resulted in the discovery of his trouble but also led to its eradication.

The too often and too loosely used term of "virus infection" for any form of pulmonary disease of which we are ignorant, is a very dangerous practice. Any form of pulmonary disease should be investigated thoroughly by all of the aids at our disposal.

Bronchoscopy today is an indispensable aid, not only in the diagnosis but also in the treatment of many types of pulmonary disease.

255 SOUTH 17TH STREET.

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XCVIII

PERFORATION OF BOTH MAIN STEM BRONCHI BY A LARGE BRONCHOLITH LOCATED IN THE SUBCARINAL REGION

UNEVENTFUL RECOVERY FOLLOWING ITS ENDOSCOPIC REMOVAL

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SCHENECTADY, N. Y.

The subject of broncholithiasis makes up one of the interesting chapters in the field of diseases of the chest. That this unusual condition is not new is proved by the historical fact that expectoration of calcareous material has been known since the time of Aristotle. In 1947, Lell,¹ in an excellent review of the subject, stated that only 69 cases had been reported. To this number he was able to add six more cases from his personal records. The addition of one more case by the author brings the total number of reported cases to date to 76.

The true definition of the term broncholithiasis is the formation of a calculus within the bronchial lumen. It is true, as has been aptly stated by Tinney and Moersch² and by Barrett,³ that long standing inflammatory processes in the bronchial pulmonary tract may lead to calcareous degeneration. However, clinical and post-mortem studies clearly indicate that the majority of calculi are extra-bronchial and develop as a result of tuberculosis of the lymph nodes which accompany the pulmonary vessels and the ramifications of the bronchi.

In the initial infection of tuberculosis the tracheal-bronchial glands are invariably diseased and may attain considerable size. The glands may undergo a process of caseous necrosis with subsequent fatty degeneration. In the further progress of this necrobiotic condition, the fat is broken up into glycerin and fatty acids, the latter uniting with the calcium in the blood to form an insoluble soap, which in turn is converted into the carbonate and phosphate of

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

calcium. According to Wells,⁴ calculi when completely formed consist of 85-90% calcium phosphate and 10-15% calcium carbonate.

The peribronchial and perivascular location of calculi may lead to perforation of a bronchus or erosion of a vessel. I feel certain that in my own experience the underlying etiologic factor in a certain percentage of cases of unexplained asthmatic wheezing, recurrent hemoptysis, massive pulmonary hemorrhage and acute bronchogenic spread of tuberculosis was due to traumatization by broncholiths.

The clinical symptoms resulting from broncholiths perforating into a bronchus are chiefly those of bronchial occlusion. They may be easily confused with the symptoms produced by a foreign body, intrabronchial neoplasm, endobronchial tuberculosis, chronic bronchitis and bronchial asthma. The severity of symptoms will naturally depend upon the degree of bronchial obstruction. In the case of the patient which I am reporting, the chief symptoms were mainly those of paroxysmal attacks of coughing with asthmatic seizures, recurrent hemoptysis and constant dyspnea.

The diagnosis of broncholithiasis is rarely made except by bronchoscopy. A valuable guide in the diagnosis is the past history of the patient having coughed up calcareous material. It would seem that x-ray studies of the chest would permit easy positive diagnosis. However, this is not true since many of these calculi are located in the hilar and subcarinal regions where they are overshadowed by the large vascular structures present in this area. Then, too, it must be remembered that broncholiths which have not undergone complete calcareous formation may show a decreased opacity for x-ray interpretation. Sectional radiography may oftentimes reveal the presence of calculi which have failed to appear in the ordinary roentgenograms. In the absence of demonstrable pulmonary pathology, broncholithiasis should always be considered in the differential diagnosis in patients presenting the above chain of symptoms. If calcific masses are present in the chest roentgenograms, it should stimulate a more thorough study and no time should be lost in submitting the patient to a bronchoscopic examination.

The following case history and findings of the endoscopic examination is the most unusual ever encountered by the author during a period of over 15 years in the practice of broncho-esophagology. The present literature on the subject of broncholithiasis fails to reveal a similar case in which a large broncholith located in the subcarinal region perforated both main bronchi.

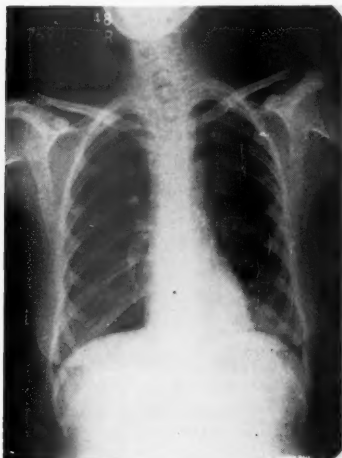


Fig. 1.—Chest roentgenogram taken 12 days before admission to the hospital showing a generalized emphysema with depression of both diaphragms and widening of the intercostal spaces. These radiologic findings strongly suggested the previously established diagnosis of bronchial asthma.

REPORT OF A CASE

S. G., a white woman aged 45, was admitted to the bronchoscopic department of the Ellis Hospital on August 14, 1948.

Her past history revealed that for the past ten years she had undergone constant medical treatment for intractable bronchial asthma associated with paroxysmal attacks of coughing with recurrent hemoptysis. During this period, she had been hospitalized numerous times with no apparent relief. The referring doctor's chief interest in recommending the patient for bronchoscopic examination was to obtain aspirated secretion from which a vaccine was to be made. The laboratory data sent along with the patient was essentially negative. Numerous chest films that had been taken during the past year revealed findings suggesting bronchial asthma (Fig. 1).

Upon her admission to the hospital the patient appeared moribund, showing evidence of marked respiratory distress which strongly suggested the established diagnosis of bronchial asthma. In view of her condition, I was reluctant at that moment to carry out the requested endoscopic procedure. However, one hour after her admission, I was suddenly called to see the patient who at this time seemed to be in greater respiratory distress. Examination of the chest revealed

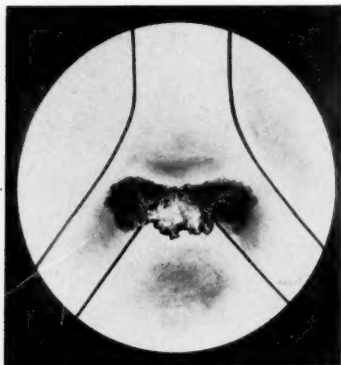


Fig. 2.—Schematic drawing showing the position of the perforating broncholith in the subcarinal region. The projecting calculus was surrounded by a mass of granulation tissue which almost completely occluded both main stem bronchi.

a marked bilateral obstructive emphysema with marked retraction in the region of the epigastrium. The breath sounds were barely audible and the percussion note throughout was hyper-resonant. Diaphragmatic excursion was not obtainable. An emergency bronchoscopy was immediately advised. There was no time for proper sedation or for the local anesthetization of the pharynx and larynx.

The endoscopic findings revealed both main stem bronchi close to the carinal bifurcation to be almost completely occluded by a granulomatous like mass of tissue (Fig. 2). The carina was flattened and some of the granulation tissue was seen to extend across its posterior portion and wall of the trachea. The slightest contact of the tip of the aspirator with this tissue caused severe bleeding. By the process of morcellation, I immediately began the removal of the obstructing tissue. As the bleeding became more profuse, I felt that I was dealing with a bilateral adenomatous involvement of the bronchi. In the process of attempting to remove the last remaining tissue from the right bronchus, my forceps came into contact with a hard object as evidenced by the grating sensation imparted to the forceps. This same grating sensation was experienced when working in the left bronchus. The diagnosis of broncholithiasis quickly flashed in my mind. The question now was how to remove the foreign body and from which side should the attempt be made. In view of the fact that the foreign body could not be visualized, partly because of decreased illumination due to accumulation of clotted blood at

the distal end of the scope, I had to be guided by the grating noise of my forceps against the foreign body. By a stroke of luck rather than by any natural ability which I possess, I was able to obtain a firm grasp of the object which was located within the inner wall of the right bronchus close to the carinal bifurcation. Keeping a firm grasp on the foreign body I pulled unusually hard, but nothing happened. I was afraid to exert greater force fearing that the forceps would break. At this point the patient was in a desperate condition and I thought the best thing to do was to give up. However, I felt that as long as I had the foreign body firmly within the grasp of the forceps that I should give it another try. Pulling on the forceps with all my strength, there was a sudden give and for a tense moment I was fearful that I had also removed a portion of the carina. However, fortunately no such thing happened. The foreign body still firmly grasped was removed in the usual manner. The type of forceps used throughout the entire procedure was a standard Jackson ball tissue forceps.

Histological examination of the removed tissue revealed granulation tissue with chronic inflammation. Special tissue staining method for tubercle bacilli gave negative findings.

The removed broncholith, pyramidal in shape, measured 1.75 x 1.5 cm in diameter. It was grayish in color, hard in consistency and pitted throughout. Close inspection of the foreign body showed that it was intact and that it had not been broken in the process of removal.

It is difficult to explain why the removal of this large foreign body which was deeply embedded in the bronchial wall did not result in mediastinal and subcutaneous emphysema or severe hemorrhage. The only explanation that I could possibly offer was that it was contained in a dense fibrous capsule.

Following the endoscopic removal of the foreign body, the patient had a stormy time for the next 24 hours. On the sixth day she was bronchoscoped again, at which time small masses of clotted blood were aspirated from both main stem bronchi. There was no further evidence of any foreign body present. On the twelfth day a lipiodol study was carried out which revealed a beginning bronchiectasis of both lower lobes (Fig. 3). She was discharged on the fourteenth day and has enjoyed good health up to the present time.

An interesting point in the possible diagnosis was that, of the numerous films sent along with the patient, no lateral films had been taken. Even if the calcific mass had been noted, I doubt very much whether I would have associated its finding with the present-

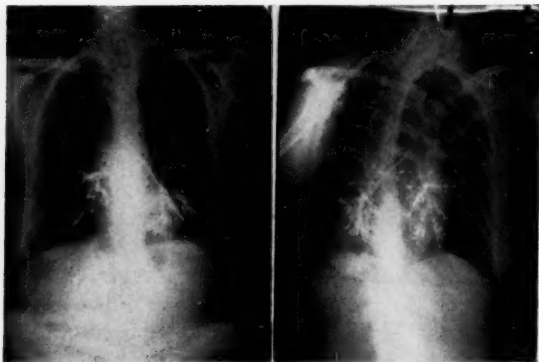


Fig. 3.—Bronchogram taken 12 days following the removal of the broncholith, showing a beginning bronchiectasis of both lower lobes.

ing symptoms. It must be remembered that a majority of the adult population will show calcific masses as a result of latent tuberculosis.

SUMMARY

It is difficult to draw any definite conclusion from this unusual case, except to show the ever increasing importance of bronchoscopy in the field of clinical medicine and surgery. I would further go on record as stating that no patient, particularly in the adult age group, should be treated for bronchial asthma unless that patient has first undergone a diagnostic bronchoscopy.

1301 UNION STREET.

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XCIX

THE EFFECTS OF AIR POLLUTION ON THE RESPIRATORY TRACT

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Let me take you back a few months, to October 30, 1948. On that day a strange, silent plague descended upon the town of Donora, Pennsylvania. With the dawn came a mysterious visitant striking terror to the heart of every man, woman and child in that industrial town. According to press reports, more than 20 persons died and over 400 became sufficiently ill to require medical treatment.

What was the cause of this terrifying phenomenon? To answer that question, let me describe to you the locale of the disaster. Donora is a town with a population of about 12,000, situated 25 miles southeast of Pittsburgh in the heavily industrialized area of the Monongahela River Valley. According to the press, a low-hanging, unusually dense smoke-fog spread over an eight-mile area about Donora, enveloping the town for a period of three days, from the 27th through the 30th of October.

It was on the third day that this mysterious plague struck. Its victims were mostly elderly persons and known sufferers from pulmonary or cardiac diseases. We know from press reports only the immediate and most severe casualties, but the entire town was affected. Physicians observed that the elderly and the already ill developed alarming symptoms simulating pulmonary or cardiac asthma, 40 of them eventually developing cardiopulmonary decompensation with pulmonary edema and circulatory collapse.

It took a disaster like this to focus our attention upon a problem peculiar to Twentieth Century man. Yet alarms had been raised before. We might have learned by the experience of others, for this was not the first such disaster. Eighteen years before, in the early part of December, 1930, a heavy fog lay for several days over a highly industrialized area in the valley of the Meuse River, in Belgium. Before it lifted, 70 persons had died, and several thousand had become violently ill. In two days, the death rate in the afflicted community was abruptly raised to 10.5 times the normal.

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

Following the Belgian disaster, an expert committee was appointed to investigate, composed of physicians, pathologists, chemists, industrial hygiene engineers. Their report presents a striking picture. Medically, it was found that the symptoms most commonly experienced included a painful irritation, often becoming acute retrosternal pain extending along the anterior edge of the ribs, attacks of coughing, dyspneic respiration of a slow, expiratory, paroxysmal nature like asthma. Patients were observed to have pale faces, rapid pulses, and laryngeal irritation. Many had attacks of nausea, vomiting and watering of the eyes. Death generally occurred through cardiac failure, again mostly affecting the aged and the already ill. Autopsies showed a diffuse congestion of the tracheal mucosa and large bronchi. Fine black granulations, subsequently identified as soot particles, were observed in the pulmonary alveoli.

What the two disasters, the Belgian and the American, have in common is this: Each occurred in a heavily industrialized valley region. Each resulted from a peculiar combination of atmospheric conditions and industrial activity. The report on the Meuse disaster states that in the period of the fog, due to high atmospheric pressure and absence of wind, smoke from the forest of factory and domestic chimneys dropped downward and mixed with the fog, laying a heavy blanket of *smog* over the region. The entire valley was thus transformed into a huge tunnel in which all the gaseous products of home heating and the residual industrial wastes were accumulated. We may surmise that a similar set of conditions prevailed in the Donora disaster. Yet these conditions are not peculiar alone to these industrialized valleys. Suppose this had happened in one of our industrial cities. If you apply the rate of death in the Meuse Valley to the city of London, about 3,200 people would die in the course of two days, resulting without doubt in severe panic among the population, with far reaching consequences.

Smog was the enemy, in these two disasters—smog, the combination of fog resulting from natural atmospheric conditions and the manmade products of industrial or domestic combustion. I am informed that the subject of atmospheric pollution has never yet been discussed before this society, nor has reference been made to it in any of the textbooks. Is it not striking and curious that we, concerned with that branch of medicine which deals with conditions of the respiratory tract, should never have concerned ourselves with the air we and our patients breathe, should never have considered together its possible effects upon health and the diseases which we, in our medical practice, attempt to heal?

Public health authorities, and the medical profession in general, are greatly concerned with purity of the water we drink. Large amounts of public money are spent on water purification, much scientific effort and ingenuity go into safeguarding our water supply. Yet the average intake of water by a human being in a day is approximately one to two quarts; daily consumption of both food and water averages only five and one-half pounds. Contrast this with the other significant intake from our physical environment—the air we breathe. Seven to ten thousand quarts of air a day enter the body of the average person; 25 to 35 pounds. Yet strangely little is known scientifically about the effects upon health of air, particularly of polluted air breathed in the course of an ordinary everyday respiration. A search of the literature reveals much attention to the economic and aesthetic consequences of atmospheric pollution; relatively little attention to the health consequences.

I have called this a problem peculiar to Twentieth Century man. Of course it became a problem with the advent of the Industrial Revolution. But it is a problem of many serious consequences in our own time, for in this nation at least we are highly urbanized, highly industrialized, a very large proportion of our people living concentrated in areas where they are exposed constantly to the waste combustion products of our factories and power installations, as well as those of our vast number of internal combustion engine vehicles. You need only to fly over one of our industrial cities, see rising high over the city a black column which seems almost thick enough to slice as your plane approaches it through the clean air of the countryside, to realize that the people in that city live under a pall which shuts them off from much of the sun's rays and which gives them only badly polluted air to breathe.

Air of our cities is polluted principally by smoke, defined as the mixture of flue gases and suspended particles of solid or liquid matter which is produced by incomplete combustion. Soot is the prime ingredient, from coal burned in industrial operations, heating plants and domestic heating equipment; and soot is largely a mixture of varying proportions of carbon, tarry products of coal distillation, sulfur acids and ash. Air is also polluted by gases from coal fires, from the processes of our manufacturing plants, and from decay of organic matter; these gases including sulfur dioxide, sulfur trioxide, hydrogen sulfide, ammonia, chlorine, nitrogen acids, carbon monoxide, carbon dioxide, and various special pollutants resulting from manufacturing.

In the Meuse Valley disaster,² findings of the industrial chemists showed that the most abundant of the irritant gases discharged

into the valley were the sulfur compounds—sulfuric and sulfurous acid and anhydrides. Sulfur dioxide was held to be the chief culprit in the disaster, with the additional conclusion that hydrofluoric acid which also polluted the atmosphere may have played a significant part. Causes of the Donora disaster have not yet been ascertained, but preliminary studies point to the sulfur compounds, with the indication that sulfur dioxide produced from coal in the ore-smelting furnaces was, by the atmospheric conditions prevailing in this time of heavy fog, gradually transformed into the deadly gas sulfur trioxide. Other medical opinion implicates fluorine, found by Sadtler³ in his analysis of the smog; and it has been suggested that the smog contained either zinc or cadmium in sufficient quantity to be toxic.

These conclusions would appear to indicate that while smoke control is of the utmost importance, it is not enough to prevent the introduction into the atmosphere of visible contaminants but that invisible poisonous fumes must also be prevented. The St. Louis program, while aimed at smoke control, achieved significant control of sulfur fumes through causing people to stop burning high-volatile bituminous coal which contains a high percentage of sulfur.

Now let us consider the health consequences of atmospheric pollution. More than 200 years ago, Ramazzini⁴ pointed out the harmful effects upon health of smoke pollution, but it was not until 1860 that Traube proved that carbon particles breathed in are deposited in the lungs, pleurae and lymph glands. While it is thought unlikely that there is a direct causal relationship between tuberculosis and smoke effects, it is true that in treatment of this disease we stress clear air and sunlight. In a study of the then extremely smoky city of Pittsburgh undertaken in 1914, it is shown that this city had the highest constant pneumonia death rate of any community in the world, and that the smokiest wards of the city had the highest pneumonia death rate. However, industrial hygiene considerations must be kept in mind when interpreting this fact, since these wards also are the habitations of steelworkers, in whom pneumonia is an occupational disease. Also in these smoke-filled wards of the city, the investigators found a striking prevalence of acute respiratory disease of many other kinds, children with discharging ears, chronic nasal catarrh.

We know that it is common in city medical experience to find our bronchitis patients dying in numbers during prolonged periods of winter fog, when the air is heavily polluted with smoke and its sulfur products. Studies in England—I cite Osborne⁵—have shown a direct causal relationship between the amount of atmospheric pollution and the death rate from diseases of the respiratory tract.

While roughly one-half of all deaths in England and Wales were due to respiratory diseases, states Osborn, at the time of his study respiratory death rates in smoky Manchester were twice as high. For rural England the infant death rate for 1928 from pneumonia and bronchitis was 8.8 while for Manchester it was 23.16. Taylor showed that the lungs of dwellers in the industrial cities are blackened both on the surface and in the depths, due to the deposit of carbon. The tarry matter and the less visible sulfurous compounds which are far more dangerous set up an irritation in the mucous lining of the trachea and bronchi. Chronic catarrh supervenes, the mucous lining becomes rough and thickened, the surrounding tissues lose their elasticity and become leathery in texture. These changes produce symptoms of chronic bronchitis, symptoms resulting from persistent irritation, partial collapse of the lungs, and incomplete oxygenation of the blood.

Another still more alarming probable consequence of atmospheric pollution is cancer of the respiratory tract. Hueper,^{6, 7} Chief of the Environmental Cancer Section of the National Cancer Institute, U. S. Public Health Service, states that industrialization in recent decades has been accompanied by the occurrence of numerous and often new types of inflammatory and degenerative diseases of the respiratory organs, and the discovery of a number of new neoplastic disorders of these tissues, as well as remarkable increase in the incidence of pulmonary cancers. Before 1900 malignant tumors of the respiratory system, especially of the bronchi and pulmonary parenchyma, belonged to the rarer types of cancer. There has been in the last 20 years a definite and striking increase of the incidence of pulmonary neoplasms, authenticated by Hueper, Wells, Simons, Weller, Hutchinson, Hraby, and Sweany. Autopsy records, which doubtlessly represent the most reliable source of information and which were obtained by competent pathologists in large and well controlled institutions, show this trend of increase in a convincing manner. It is Hueper's opinion that there has been at least a tenfold increase since the turn of the century.

Townsend, Chief of the Industrial Hygiene Division of the U. S. Public Health Service, declares that while no authenticated facts yet exist incriminating smoke pollution as the cause of respiratory neoplasms, it is safe to assume that since smoke contains tars and tar is a carcinogen, there is some relationship. This is borne out by the high rate of pulmonary cancers among workers in industrial processes where there is exposure to tar. Studies made in Germany and the United States show 18 to 50 times the normal rate of lung cancer among workers in the chromate industry, and the chromates

are a not unusual atmospheric pollutant. It is Hueper's belief that persons living in the immediate vicinity of chromate plants also must be affected in this way. Other factors in the atmospheric conditions surrounding certain industrial plants are held to be conducive to respiratory malignancy. It has now been definitely proven through laboratory study that cracked oils are very high in carcinogenic hazards, causing lung cancers as well as skin cancers. A new factor has entered the situation with the intensive development of radioactive processes. Evidence has come from Germany and Czechoslovakia that in radioactive mines, 80% of all deaths among the underground miners were caused by lung cancer.⁸ Other industrial processes in which tiny particles of noxious substances are emitted into the surrounding atmosphere are further implicated in the rapid increase of malignant neoplasms in our population. It has been demonstrated that smaller particle size is much more deadly in causing cancer. Particles of the order of less than one micron are absorbed deep into the lungs. This process brings down sharply the latency period of the neoplasm. The period when the cancer lies dormant has been shown to drop from 15 to 5 years as a result of this factor.

All this evidence can lead to but one conclusion. There must be *research* and there must be *control*. In the case of the Donora disaster, investigation is now being carried on by the U. S. Public Health Service, to determine exactly what happened and why. An Industrial Hygiene Division team consisting of physicians, nurses, engineers, statisticians and veterinarians are at work in that area, finding out what materials go into its industrial processes and what comes out of the smokestacks, and the effects of these products upon people and animals. This study should provide a basis of factual information leading to scientific prevention of similar accidents—if the medical profession as well as the general public are sufficiently insistent that such prevention take place. Other studies are being made of the effects of specific atmospheric pollutants upon general health, upon the incidence of cancer of various types, upon respiratory diseases. We must study, we must know the facts; and we must insist that the knowledge gained be put to use in protecting our population from unnecessary health hazards.

SUMMARY AND CONCLUSIONS

1. An accident occurred at Donora, Pennsylvania, October 30, 1948, in which 20 persons died and hundreds were made ill, as a result of smog containing some toxic substances. This was similar to a disaster in the Meuse Valley of Belgium in 1930, held upon investigation to be caused by combustion products in the atmosphere.

2. Smoke control legislation is necessary in the public interest. Many of our cities have such legislation, but enforcement must be intensified, and where necessary better legislation must be adopted leading to control of the toxic invisible as well as the obvious products of combustion, from factories, domestic heating plants, and railroads.

3. Authorities declare that adequate environmental control measures are possible, both as relates to industrial as well as domestic combustion products.

4. Serious effects upon respiratory health have been demonstrated by numerous scientific studies of atmospheric pollution. The cause-effect relationship between abnormally high death rates from pneumonia and smoke polluted air is unquestionable. Inflammatory diseases of the respiratory tract in general may result from chronic irritations by air pollutants.

5. Cancer of the lungs, the larynx and other parts of the respiratory system may be caused by atmospheric pollution. There has been tremendous increase in the incidence of such malignancy since the turn of the century, with the heavy industrialization of many countries including our own.

6. It is a public duty of our branch of the medical profession, as well as the profession as a whole, to become more informed about the hazards to health of atmospheric pollution, and to insist that the proper public action be taken.

711 S. JEFFERSON STREET.

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C

PHYSIOLOGICAL RESPIRATORY CHANGES ASSOCIATED
WITH BRONCHIAL INFECTION

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AND

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Infection of the bronchi is such a common thing that little attention is paid to it unless it is acute or troublesome by nature of its severity. The ordinary mild disease is thought of as a natural occurrence, and as such is tolerated without any thought of serious consequences. In the course of our investigation of this common disease, it developed that changes of varying degree of severity in the ventilatory mechanism and even in the entire function of respiration occurred by reason of the severity of the infection, as might be expected, or because of its chronicity, which was not anticipated.

The bases of these changes are well known and long recognized factors in the physiology of the bronchi and lungs. The first of these is the well known mechanism of elongation and widening of the bronchus during inspiration, and narrowing and shortening of the bronchus during expiration. This is clearly observed through the bronchoscope and on the x-ray film with the use of a contrast medium (Fig. 1 and 2). It may be noted that the iodized oil which simply lines the bronchial wall during inspiration completely occludes the lumen during the sharp or forced expiration. This latter phenomenon is common in the presence of bronchitis and bronchiolitis. Not only are the bronchial walls red and irritated, creating a greater degree of contraction which may result in spasm, but there is present in all cases a greater or lesser degree of secretion which offers some degree of obstruction to the passage of air through the bronchi.

This can be shown by tracings on the spiogram. In the normal individual there is a smooth tracing which, when the patient is asked to breathe as rapidly as possible, increases in amplitude and

From the Chest Service of Michael Reese Hospital, Chicago, Illinois.

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

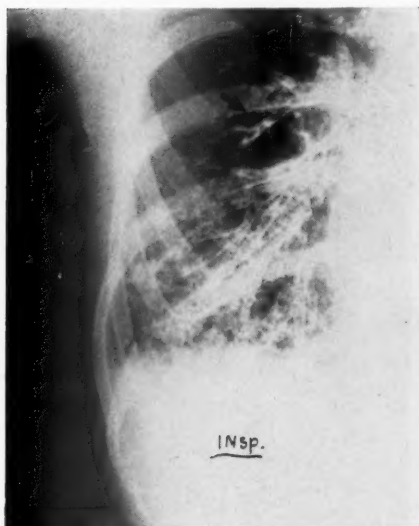


Fig. 1.—Bronchi during inspiration.

rate as the demands of increased ventilation are placed upon the bronchial conduction system. However, if there should be any bronchial infection or other mechanism creating irritation or secretion in the bronchial lumen, the curve is quite different. We find the same smooth tracing in normal respiration, but when the patient is asked to breathe rapidly a very different picture is seen. Air gets in through the bronchi without difficulty, but during the sharp expiration, it does not get out as easily. The result of this uneven conduction is the trapping of air within the chest, which may result in the entrapment of as much as 1400 cc in 15-20 seconds of rapid respiration. We believe that this is caused by bronchial spasm or other mechanism of obstruction during expiration, probably in the region of the bronchioli.

In order to prove this we selected a patient who was a known asthmatic, but who had neither wheezing, dyspnea or other symptoms of asthma at the time of testing. He was asked to go through the above test, and it was only after some difficulty that we were able to persuade him to do this. In the beginning, he took one deep inspiration, was unable to exhale any air, tore the tube from his mouth and claimed he was asphyxiated. After considerable persuasion we secured a normal tracing, and then in rapid respiration,

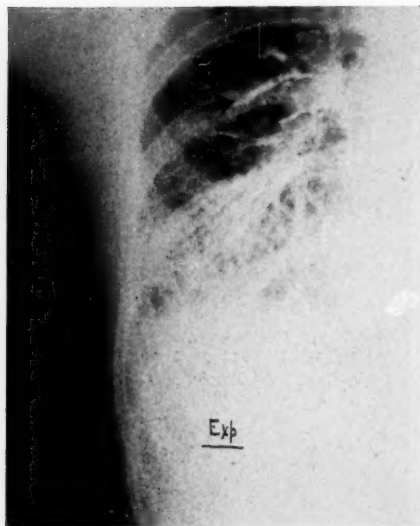


Fig. 2.—Same case as Fig. 1. Bronchi during expiration. Note (arrow) typical bronchus occluded during expiration.

the entrapment of a considerable volume of air. This returned to normal levels when breathing was itself normal once more. At this point we injected aminophylline intravenously and allowed the patient to rest for five minutes while normal tracings were being taken. At the end of this time we again requested the patient to breathe rapidly and a very small amount of trapping was the result. Eight minutes after injection of aminophylline this patient was again tested and his curve on rapid respiration was entirely normal, showing no entrapment (Fig. 3). This indicated that the mechanism of entrapment of air was a function of bronchial disturbance and that it bore a direct relationship to the amount of bronchial irritation and secretion, as well as the rapidity of respiration.

In a great many tests we found this conclusion to be borne out. Trapping of air bore no relationship to vital capacity and was frequently observed in individuals with minor bronchial infections who had not demonstrated this phenomenon before the development of this inflammatory process. Varying degrees of entrapment were found. In some cases of very long standing infection, rapid respiration produced obstruction on inspiration as well as expiration resulting in the cessation of ventilation for all practical purposes.

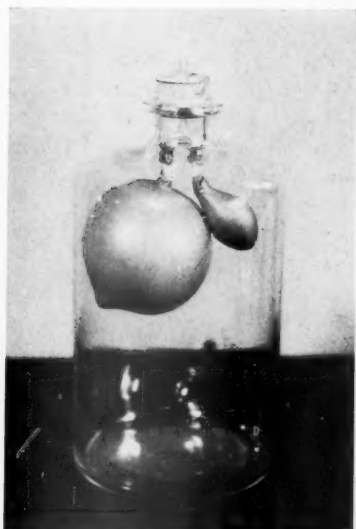


Fig. 3.—Uneven expansion of two balloons in vacuum bottle caused by very slight differences in elasticity.

This mechanism, which is present in all bronchial infection, explains why some patients who are perfectly comfortable at rest or during normal mild activity, may show extraordinary dyspnea following activity that results in a marked increase of the respiratory rate. Some of these people show an amount of respiratory disability quite out of proportion to that which is anticipated and the blame is generally placed on advancing age, weakened myocardium, or increased weight, when the inability of the chronically infected bronchi to handle increased ventilation and rapid breathing is the actual cause. This is the earliest and the first of the physiological disturbances which is produced by bronchial infection and is found to some degree in every such disturbance.

If the infection lasts long enough, and this does not have to be for many years, further changes occur. Chronic bronchial infection is largely submucous and as such it infiltrates along the bronchioli into the interalveolar septa. This is seen as an increase in round cells and intercellular secretion. The result is loss of elasticity in the involved area which, in the early stages at least, is very slight. Little attention has been paid to this change because the lung is ventilated

in an apparently normal fashion. No changes are seen on the x-ray film.

However, as was first pointed out by Ornstein, very slight changes in elasticity may cause marked irregularity in ventilation. This can be demonstrated by the use of two balloons. We have repeated this experiment many times using every type of balloon as well as latex condoms. The results were always the same. The balloon which is most elastic expands first. Sometimes it is completely expanded before there is much expansion of the less elastic one. In the expiratory mechanism, the same inequality of contraction takes place. It is obvious that what is true for the balloons should be likewise true for the lungs, and that very slight changes in elasticity should produce changes in ventilation. This would result in the most elastic areas of the lung expanding first, and the less elastic areas only being called into play when respiration is deeper. Proof of this mechanism was found in the study of expired air.

We have been in the habit of analyzing the gases in expired air by taking eight samples, two seconds apart, throughout expiration. The sampling is begun after 500-1000 cc has been expired during the complete expiratory effort. This, when plotted on the graph yields a reasonably straight line running from 17% to approximately 11% at the end of expiration. This is the result in normal patients. In the presence of bronchial infection where we anticipated some ventilatory inequality, a very different curve was seen. Instead of the smooth sloping line, our curve is irregular with recurrent peaks. We believe this to indicate areas of unequal elasticity. As one area contracts, the gas expired decreases in oxygen content. Then as an area of different elasticity begins to contract with its higher oxygen concentration, the peak is found representing the resultant between the low oxygen of the first area and the higher oxygen of the second area. Then another major area may begin and an irregular curve with numerous peaks is the result. This is the regular picture of the expired air in cases of long standing bronchial infection. Its interpretation as regards function is not very difficult.

Since ventilation and circulation go hand in hand, it follows that the area that is not ventilated during normal respiration has likewise a very small share of the pulmonary circulation. Thus when greater demand is placed upon the lung and it becomes necessary to increase ventilation, these areas are called into play but their function is far from efficient. This is another explanation of the sudden and extreme disability which these patients show on extraordinary exertion.

These two above mentioned changes in the normal physiological function of the respiratory mechanism are the cause of serious, if frequently unrecognized, disability. In many cases of sufficiently long duration or in diffuse infection another and more serious change occurs. This is thickening of the alveolar wall caused by cellular and intracellular elements and the eventual development of fibrosis in these areas. The end result is, of course, emphysema. These changes are for a long time microscopic even as are the alveoli, and do not produce a recognizable picture of fibrotic lung on the x-ray film. They do produce some interference with the passage of oxygen across these thickened alveolar walls.

In periods of normal breathing with normal amounts of oxygen in the inspired air, no change in the oxygen saturation of the arterial blood is noted. However, during long drawn out expiration, or rapid ventilation with entrapment of air, or when breathing an atmosphere deficient in oxygen, there is a very marked change between such individuals and normal persons. This can be measured experimentally by having the patient breathe an atmosphere of 11% of oxygen. In the normal person there is observed a drop in the arterial oxygen saturation to around 90% with a very slow decrease during the four-minute period, to approximately 82% at the end of this time. In the above mentioned type of case, however, inspiration of a similar low oxygen atmosphere caused a rapid drop to below 90% and an irregular decrease ending at the level between 65 and 70% saturation at the end of four minutes. This is a most serious change, being irreversible and being associated with, or a forerunner of, the pulmonary hypertension which results in cor pulmonale.

When we review the material just presented, it becomes apparent that we are not dealing with three isolated and independent manifestations or sequelae to bronchial infection. What we have described are various stages in the single process, the course of which may extend over many years. Thus it would seem that the ordinary bronchial infection is not a complaint but a serious disease, if we consider its effect rather than its symptoms. Like many another condition, its seriousness is only apparent when it is too late to do anything about it.

In the light of this information it becomes essential to treat this condition at the time when it is still reversible and no extensive or permanent changes have taken place. With our present knowledge of the use of antibiotics, especially by the aerosol method, the establishment of adequate drainage and the removal of causative factors,

we should be able to control all cases of bronchial infection in a reasonably early stage.

We should like to emphasize once more that until the latest stage is reached, that of actual emphysema and fibrosis, disabling symptoms do not occur at rest or during normal activity. Since the mechanism of disability has been observed by experimental methods and is seen clinically when exertion or emotion causes hyperventilation, we should not be lulled into a sense of false security by the absence of symptoms, but consider every case of infection of the bronchi, regardless of how mild it may be, as a case requiring definitive treatment.

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CI

BRONCHOPULMONARY ANATOMY FROM THE BRONCHOSCOPIC VIEWPOINT

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The concept of the bronchopulmonary segment may be said to date from the writings of Ewart,¹ whose classic treatise on *The Bronchi and Pulmonary Vessels* was published in London in 1889. However, little attention was paid to this concept and little or no clinical use of it was mentioned in the literature until the paper of Kramer and Glass² presented before this Society in 1932. This paper was a combined bronchoscopic and surgical study dealing with the diagnosis, localization and external drainage of pulmonary abscess. The authors sought "to establish a smaller and more accurate unit of localization than the lobe" and they described the bronchopulmonary segment as "not only an anatomic, but also a pathologic unit," and pointed out the importance of identification of the various segmental orifices and knowledge of the size, shape and topographic position of the outer surface of each associated segment on the chest wall. In an anatomic study of 80 pairs of human lungs, they found the lobar and segmental branches to be constant in 85% of the cases and they named these segments and their corresponding bronchi, using a simple nomenclature based on their position in the lung. Furthermore, with specific relation to the problem of pulmonary abscess, they found that "practically all putrid abscesses have a definite position in one of these bronchopulmonary segments," and emphasized the fact that the bronchoscopist holds the "key position" for information concerning bronchopulmonary suppurative disease." The theoretical and the laboratory studies in this paper were further supported by clinical data concerning 12 cases of pulmonary abscess all studied bronchoscopically, but all treated surgically.

Two years later, in 1934, there appeared a paper by Nelson³ likewise calling attention to the importance of the study of bronchial anatomy in the management of pulmonary abscess, but particularly with respect to position for postural drainage. He pointed out the

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

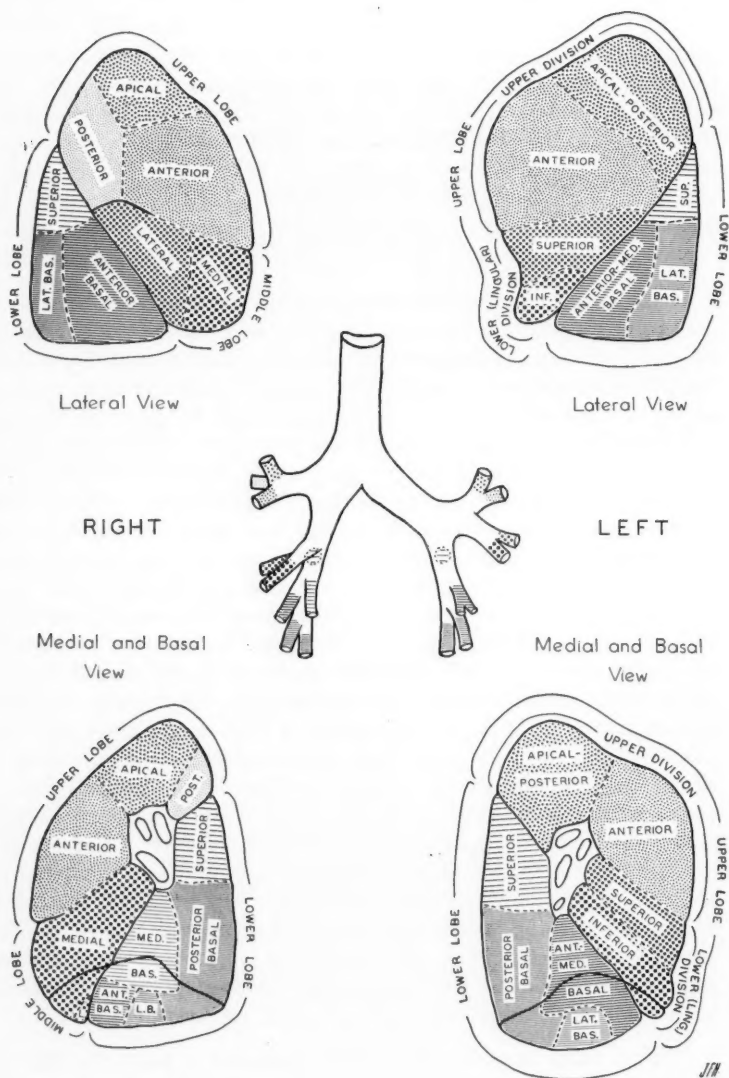


Fig. 1.—Diagram of segmental bronchi and bronchopulmonary segments, showing the Jackson-Huber Nomenclature. A slightly modified, tinted version of this chart is to be found in the current (25th) edition of Gray's Textbook of Anatomy.

advantage of continuous postural drainage in a correct position over intermittent postural drainage of the kind generally practiced without regard to the anatomical direction of the bronchus draining the abscess or the location of its orifice and its relation to other orifices. He stated that postural drainage attempted without consideration of these facts was not only valueless, but dangerous.

J. Hardie Neil⁴⁻⁶ has contributed a number of valuable papers on this subject, the first published in 1936, in which he pointed out that "bright illumination of a field by the Jackson bronchoscope is of little use to one with a misty conception of bronchial anatomy." He brought to bear a large experience in comparative anatomy as well as human, and a keen clinical sense. One of his outstanding contributions was a composite perimetric perspective diagram representing the position and relations of the various segmental orifices as seen by the bronchoscopist.

I wish to pay personal tribute to James Hardie Neil because it was his work, and especially his personal demonstration of the bronchopulmonary segment at the third Pan-Pacific Congress in Honolulu in 1939, which convinced me of the vital importance of the study of practical bronchopulmonary anatomy in the daily work of the bronchoscopist and bronchologist. Immediately after my return from the Pan-Pacific Congress, I got in touch with Dr. F. Huber, of the Department of Anatomy of Temple University, and we then began our joint study of the subject. In a paper⁷ read in 1942 and published the following year we reiterated what others had said concerning the importance of the study of applied anatomy of the bronchi and lungs, and particularly the significance of the concept of the bronchopulmonary segment. We suggested that the lungs be thought of as subdivided according to bronchial distribution, rather than according to fissures, because the former are more constant, and because this conception affords a sounder basis for understanding the physiology and pathology of the bronchi and lungs. After prolonged laboratory and clinical studies, we returned to the literature and reviewed all the systems of nomenclature that had been suggested by the numerous authors who had now contributed to this subject, and we decided that we very definitely wanted to work out a new terminology, because none of those previously suggested satisfied us. We sought "a standard clinical terminology which will be acceptable to the bronchologist, the thoracic surgeon, and the radiologist, and which will meet with the approval of the anatomist." I will not discuss in this paper the reasons for the selection of the various terms because, for that, the original paper may be consulted. The nomenclature which we suggested was as follows:

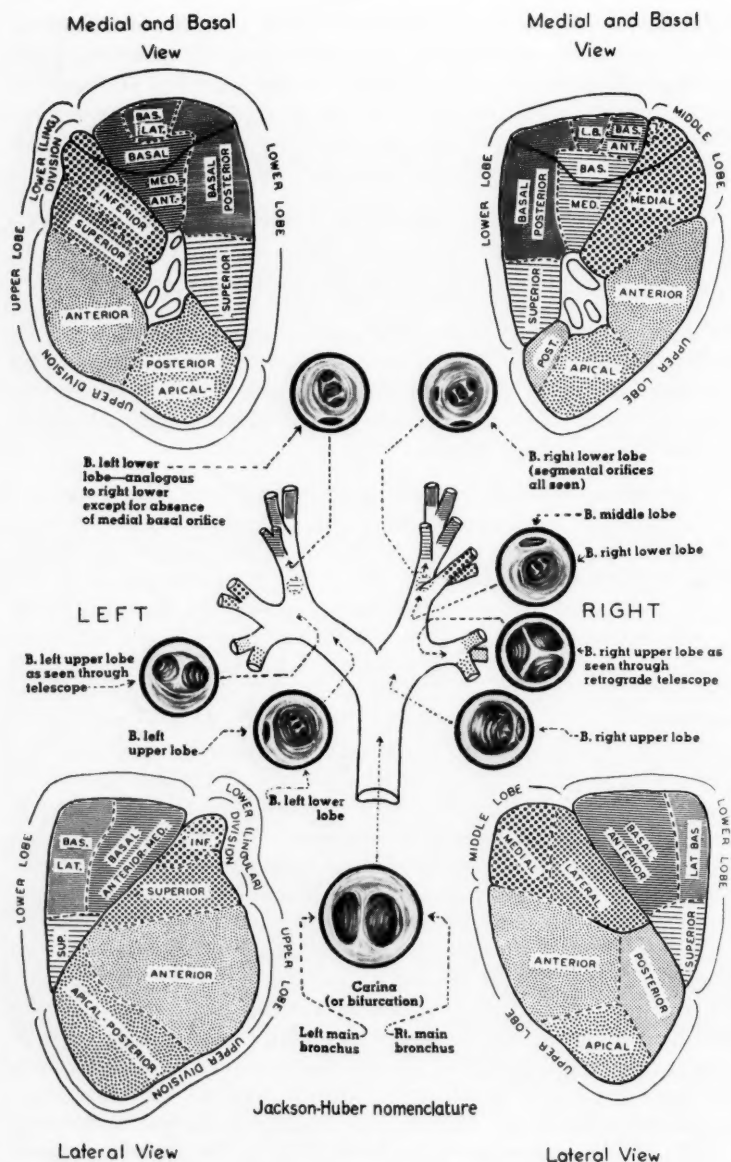


Fig. 2.—Diagram of the tracheobronchial tree showing segmental bronchi and bronchopulmonary segments, as well as the endoscopic landmarks. This chart is placed in the inverted position, showing the various structures in the same relation as they are seen at bronchoscopy.

LOBES	SEGMENTS	LOBES	SEGMENTS
Upper	{ Apical Posterior Anterior	Upper	{ Upper Division { Apical-posterior Anterior
Middle	{ Lateral Medial	Lower (Lingular) Division	{ Superior Inferior
Lower	{ Superior Medial Basal Anterior Basal Lateral Basal Posterior Basal	Lower	{ Superior Anterior-medial Basal Lateral Basal Posterior Basal

This nomenclature (shown also in Fig. 1) has met with an unexpectedly wide acceptance by anatomists (Boyden,⁸ Grant⁹) and clinicians of various specialties (Overholt,¹⁰ Scannell,¹¹⁻¹³ Wishart¹⁴). Some of the comments concerning it are quoted in the report of the Committee on Nomenclature¹⁵ of this Society presented at last year's meeting and published in the Transactions (1948). Gray's Standard Textbook of Anatomy¹⁶ has adopted the terminology for its current (25th) edition (Fig. 1). At the recent meeting of the American Association for Thoracic Surgeons in New Orleans this terminology was officially approved.

Nomenclature is important, and the general adoption of one set of names would certainly lead to better understanding of the literature, but even more important is the understanding of the anatomy itself. To the bronchoscopist the subject is important in two ways: First, a knowledge of the topographic anatomy enables him to tell from the roentgenograms, and particularly from the lateral roentgenograms, how to chart his course in the bronchoscopic approach to a lesion or a foreign body; secondly, such knowledge enables him, when he looks through the bronchoscope, to interpret the endoscopic findings intelligently, since he will know, when he looks at a certain branch bronchial orifice, just what direction its bronchus takes, and what the size, shape and relations of its tributary segments are, and how to word his report so that it will be of value to the referring physician or surgeon, and will fit in with the reports of the other clinicians and the radiologist.

Let us review briefly the endoscopic landmarks: First, of course, we have the vertical carina or bifurcation, well known to all of us, then, almost opposite it, to the right, the also vertical right upper lobe spur and the orifice of the right upper lobe bronchus. The segmental subdivisions of this (apical, anterior and posterior) cannot be seen without the use of a right angle or retrograde telescope,

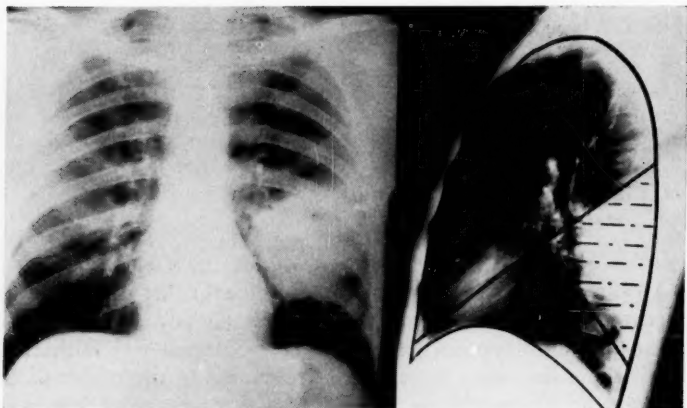


Fig. 3.—X-ray films showing pulmonary abscess, localized to superior segment of left lower lobe. This is a common site of abscess.

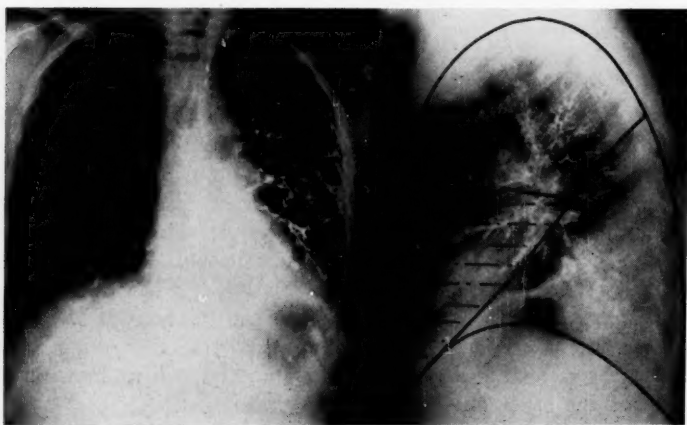


Fig. 4.—X-ray films showing bronchiectasis of the left lower lobe with associated bronchiectasis of "lingular" segments of the left upper lobe.

except in patients with atelectasis of the middle and lower lobes, or who have had the middle and lower lobes removed. However, as Brock¹⁷ has stated, "the use of telescopes for improving vision is no longer a luxury, but is a necessity for a proper and complete examination." An excellent study of the right upper lobe bronchus from the bronchoscopic viewpoint has been made by d'Hour, Devin and Langeron.¹⁸ As shown by them (and by Brock) the pattern of subdivision of the segmental orifices (Vigio) varies somewhat, but in the majority of cases (29 out of 40, or 72.5%) assumes a standard three-way pattern, the three segmental orifices going off together in a trifurcation, and all appearing about equal.

The transverse middle lobe spur on the anterior wall, anterior to which the middle lobe branches go off, is a well known landmark, but less frequently seen is the segmental subdivision of this bronchus into its medial and lateral segments. The author differs from Brock in his opinion that the foroblique telescope is of little use, because it seems to him that this telescope gives the best view into the middle lobe bronchus and almost always permits visualization of this segmental spur. In the lower lobes, almost always the five (four on the left) segmental orifices can be seen without a telescope (Fig. 2). The left upper lobe bronchus can be studied to advantage by both the foroblique and the right angle telescopes (Fig. 2).

Summarizing the clinical importance of consideration of bronchopulmonary anatomy, and particularly the segmental concept:

1. In abscess, such study facilitates both external surgical drainage and postural drainage, as well as endoscopic drainage and the endobronchial instillation, by means of a catheter or bronchoscope, of penicillin or other drugs.¹⁹

2. Bronchiectasis is, as emphasized by Overholt and others, a segmental disease, and segmental resection is the order of the day, especially in bilateral cases. Economic resection of only the diseased segments after careful complete mapping of all segments of both lungs can often be done in cases which would have been deemed inoperable a few years ago. In 60% of the cases of left lower lobe bronchiectasis the adjacent segment of the upper lobe must be removed along with the lower if the patient is to be cured.

3. In tumors, early diagnosis is made by bronchoscopy if the lesion is detected when it is segmental, causing only a segmental atelectasis, and though cure may require removal of the entire lobe or even the lung, if the tumor is malignant, cure will more likely be secured, than if diagnosis is not made until the whole lobe or the whole lung is atelectatic. As Foster-Carter²⁰ has well stated, "per-

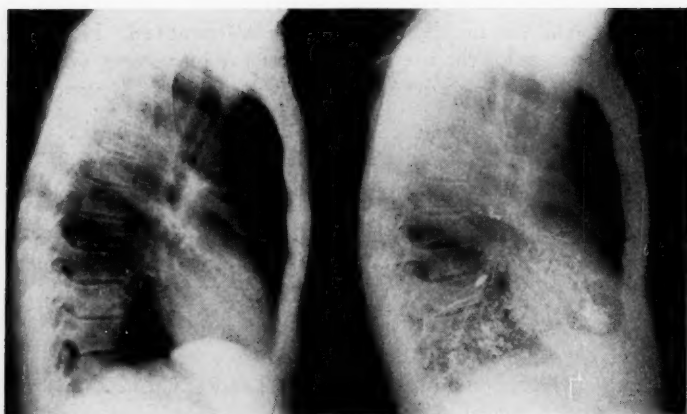


Fig. 5.—X-ray films in a case of carcinoma of right lower lobe in a male 50 years of age. Segmental atelectasis of posterior basal segment is seen in film at left and obstruction of segmental bronchus is clearly demonstrated by bronchogram at right. Point of obstruction was just beyond range of visibility in ordinary bronchoscopic examination but introduction of a small forceps into the posterior segmental bronchus rendered possible the securing of tissue which showed squamous cell carcinoma Grade II. Successful resection was carried out in this case and there has been no recurrence or metastasis in almost five years. (Case of Dr. Charles Norris, Chevalier Jackson Clinic, Temple University Hospital, reported in "Diseases of the Chest," Vol. XIV, No. 2, March-April, 1948.)

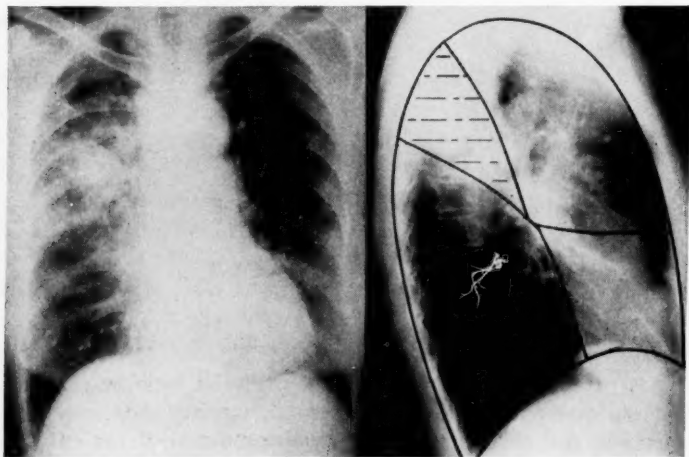


Fig. 6.—X-ray films showing tuberculosis involving posterior segment of right upper lobe. Diagnosis was proven by bronchoscopically removed specimen. This segment is a favorite site of tuberculosis.

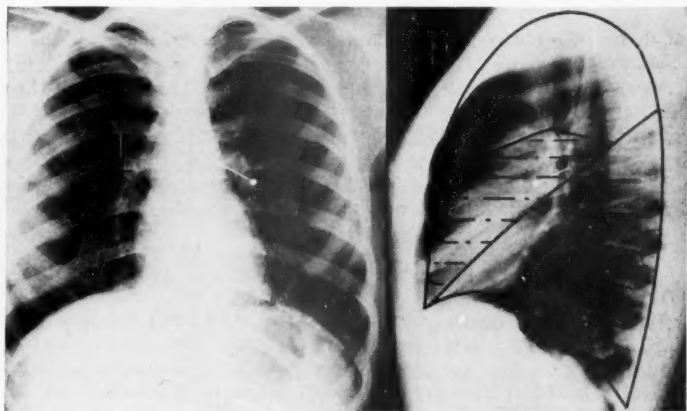


Fig. 7.—Foreign body (shawl pin) shown by lateral roentgenogram to be located in the inferior segmental branch of lower division of left upper lobe bronchus. This foreign body was removed by fluoroscopically guided bronchoscopy.

haps the most important contribution [of the segmental concept] to diagnosis is that recognition of a segmental lesion directs attention to the condition of the related bronchus."

4. In tuberculosis the sites of predilection are found to be not the apical but the posterior (or subapical) segment, and the superior (or apical) segment of the lower lobe. Much light has been thrown on the pathogenesis of tuberculosis by the application of the modern anatomical concepts to the study of the disease, which, as pointed out by the distinguished Argentine phthisiologist Sayé²¹ should be thought of as a tracheobronchopulmonary disease.

5. In cases of foreign bodies, a knowledge of the segmental anatomy is of vital importance, and removal of a foreign body in the air passages should not be attempted without accurate lobar and segmental localization, using anteroposterior and lateral, and if necessary oblique roentgenograms. Such study has explained mysteries of inability to reach foreign bodies seemingly easily accessible, by showing that instead of being in the main bronchus as it appeared to be in the anteroposterior film, the foreign body was really in a segmental branch, as clearly shown by intelligent comparative study of a good lateral film.

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CII

OPTICAL AND VISUAL AIDS TO BRONCHO- ESOPHAGOLOGY

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At times it may be pertinent to review mechanical and visual developments in our specialty of broncho-esophagology, first to determine whether proper use is being made of these developments, and secondly that by a review of these aids or helps, other important aids may be suggested or developed.

The protection of the operator's eye, first by the use of glasses, and then by the round glass shield introduced by Mr. V. E. Negus of London, is most important. If sterilized and warmed, this shield permits a clear view of the operative field, the shield being rotated when the area of central vision becomes fogged or clouded by bronchial secretions (Fig. 1).

The tip down glasses, made famous by the late Dr. Edward B. Dench, are of interest only to presbyopics. A correction for 40-50 cm can be made, and to this correction is added the additional correction for close work in laryngoscopy, 20-25 cm (Fig. 2).

Penta¹ has described ingenious glasses for bronchoscopy, which are heated to prevent fogging, and Lloyd,² in a recent paper, has described ingenious bronchoscopic glasses that are a combination of the tip down glasses and also of the Negus shield.

Any device that will keep the central visual field of our glasses or shield clear will also be of help towards a clear observation of normal or pathological conditions of the air passages. A stream of compressed air, when blown at right angles across the proximal end of the bronchoscope or laryngoscope, 10 or 15 lb. pressure, bends and deviates the warm, moist, exhaled air away from the direct line of vision (Fig. 3). This prevents the fogging or clouding of central vision.

In cases with profuse bronchial secretions, a large sponge is attached to the bronchoscope, opposite the blower tube, and secretions are blown into and collected in this sponge (Fig. 4).

The upper lobe bronchi lead to about one-half of the total pulmonary field. A clear vision and a careful inspection of these bron-

chi is mandatory in certain cases. The top telescope (Fig. 5) gives a clear view of the upper lobe bronchi and their divisions. The central telescope gives a retrograde view, and is used for inspection of the under side of tumors of the larynx, trachea or primary bronchi. The bottom telescope gives a forward and magnified view of objects ahead. This telescope can also be used with special forceps for exact removal of tissue (Fig. 5 and 6). Figure 6 shows enlarged distal ends of adult telescopes, and Fig. 7 and 8 show child-size telescopes and distal tips to be used through 4-mm bronchoscopes.

Magnification ($2\frac{1}{2}$ -3 times) can be of great help in the diagnosis of pathological changes in the air and food passages. Figure 9 shows a proximal magnifier, and Fig. 10 shows its attachment to an 8-mm A.C.M.I. bronchoscope; it can also be used with the esophagoscope and laryngoscope. When the magnifier is attached to bronchoscopes or laryngoscopes, a blower must also be used to prevent clouding or fogging of the lenses.

It is hoped that, as stated at first, the re-enumeration of these aids to broncho-esophagology may not only aid in the treatment of patients, but may suggest other developments that will be of greater use.

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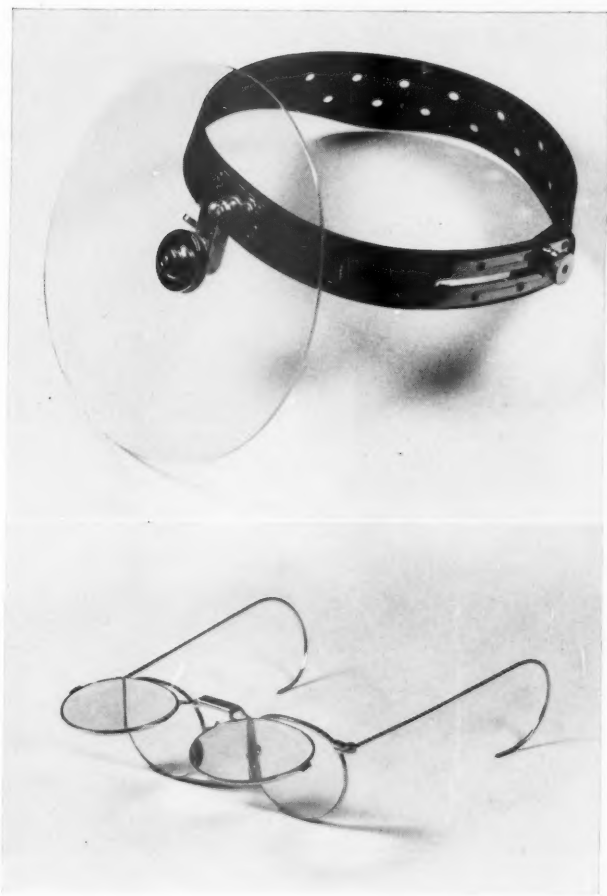


Fig. 1.—V. E. Negus shield. When central visual area is fogged or clouded by secretions, shield is rotated.

Fig. 2.—Tip down glasses, with increased plus sphere for close vision (laryngoscopic).

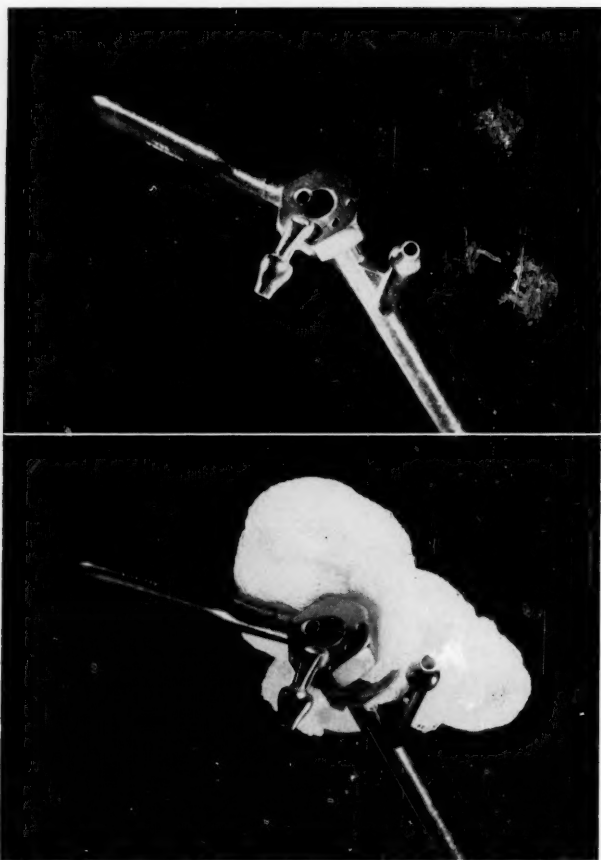


Fig. 3.—Anti-fog device. Compressed air blown at right angles across proximal end of bronchoscope deflects expired air.

Fig. 4.—Showing sponge attached to proximal end of bronchoscope equipped with anti-fog device so that secretions are blown into sponge.

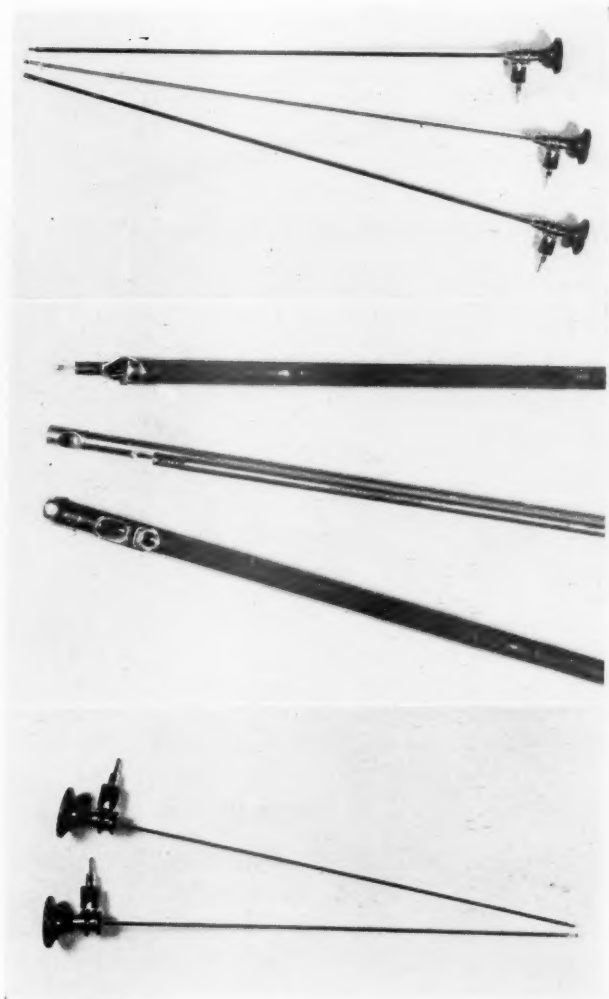


Fig. 5.—Telescopes to give increased vision. *Top*: Right angle view clear vision of upper lobe bronchi; *Center*: Retrograde view; *Lower*: Forward view with magnification.

Fig. 6.—Showing distal tip of telescope. *Top*: Right angle; *Middle*: Retrograde; *Lower*: Forward.

Fig. 7.—Small telescopes to be used in 4-mm sized tubes. *Top*: Forward view; *Bottom*: Right angle view for upper lobe bronchi.

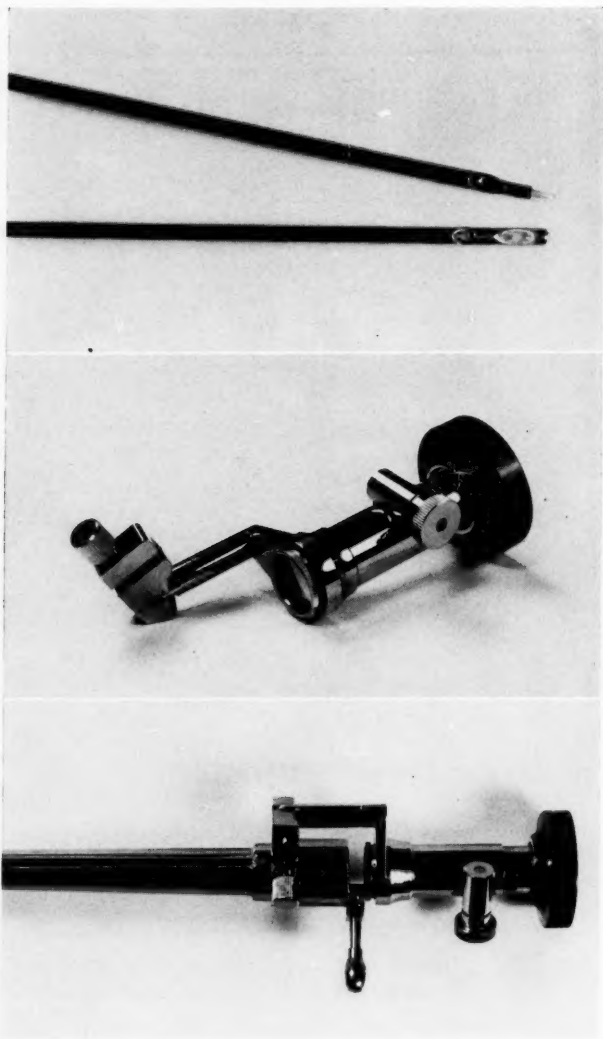


Fig. 8.—Distal tips of child-size telescopes.

Fig. 9.—Proximal magnifier for attachment to A.C.M.I. esophagoscope, bronchoscope and laryngoscope.

Fig. 10.—Showing proximal magnifier attached to A.C.M.I. bronchoscope.

CIII

SURGERY OF THE ESOPHAGUS

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AND

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Although cancer of the thoracic esophagus was first successfully treated by Torek²⁸ in 1913, this lesion was considered not amenable to surgical extirpation by most physicians until relatively recently. The procedure which Torek used in his successful case consisted of extirpation of the thoracic esophagus with the production of a cervical esophagostomy and a gastrostomy for feeding. Although subsequently these two openings were connected during eating by means of a rubber tube the digestive tract was never re-established. Adams and Phemister¹ were the first in the United States to perform successfully an esophagogastrrectomy with the re-establishment of the continuity of the digestive tube. With the introduction of this newer technique, curative resections of the esophagus have become possible and there has developed an entirely new outlook for these otherwise unfortunate individuals.

Although malignant lesions of the stomach and rectum occur more frequently than those in the esophagus, involvement of this viscus occurs frequently enough that esophageal carcinoma is of considerable clinical significance. According to Pack,²⁵ 10% of all malignant tumors of the esophagogastrintestinal tract involve the esophagus and the cardiac end of the stomach. There is probably some geographic variation in the incidence of esophageal malignant lesions. In Switzerland, according to Renaud,²⁷ 10% of all carcinomas involve the esophagus and 16.2% of males with malignant

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Read before a combined meeting of the American Broncho-Esophagological Association and the American Laryngological, Rhinological and Otolological Society, Chicago, Illinois, April 19, 1949.

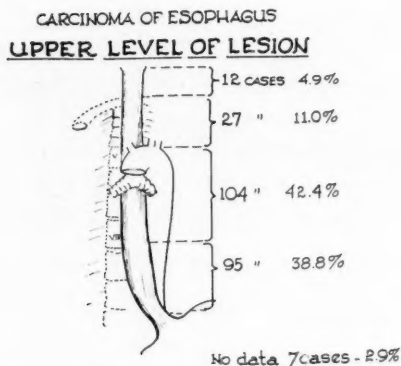


Fig. 1.—Location of lesions by anatomic level in carcinoma of the esophagus.

disease have esophageal involvement. In the United States Hoffman¹⁰ found that the number of deaths per hundred thousand population increased from 1.0 in 1915 to 1.7 in 1932. The ratio of carcinoma of the esophagus to all malignancies increased from 4.4% in the period 1920 to 1923; to 5.9% from 1924 to 1927 and to 6.1% from 1928 to 1931. These incidences in Chicago were 5.1%; in Boston, 5%, and in New Orleans, 2.3%. Carcinoma of the esophagus ranks as the ninth most frequent malignant tumor occurring in the white male.⁶ In the United States the reported deaths from cancer of the esophagus increased from 2,243 to 2,949 from 1933 to 1944, an increase of approximately 30%.

Carcinoma can involve any portion of the esophagus but the thoracic and abdominal portions are most frequently affected. Janeway and Green¹² in a collected series of 1,670 cases of esophageal carcinoma found that the cervical esophagus was involved in only 15%. We²² found that in a series of 8,572 collected cases the thoracic and abdominal portions of the esophagus were involved in 80%. However, the site of involvement varies in individual statistics. Camiel and Loewe² in a consecutive series of 30 cases of esophageal carcinoma admitted to Brooklyn Cancer Institute found that the upper portion (cervical) of the esophagus was involved in 43%. Since lesions involving these areas are best attacked through the thorax, most of the advances in the treatment of these lesions have been made by thoracic surgeons.

The present investigation is based upon a series of 244 cases of esophageal carcinoma admitted to the Charity Hospital in New Or-



Fig. 2, Case 1.—Fluoroscopy of double carcinoma. Lesion of mid-thoracic esophagus visualized, and the lesion of the distal end of the stomach not visualized.

leans and the Ochsner Clinic. In this series, only 5% were in the cervical area, 11% were in the upper third of the thoracic esophagus, 42.4% were in the middle third, and 38.8% were in the lower third (Fig. 1). There were two cases with two lesions, one with both independent lesions in the esophagus and another with a lesion in the midthoracic portion of the esophagus and a concomitant carcinoma of the gastric pylorus. The last is unusual enough to justify a short description.

REPORT OF A CASE

CASE 1.—S. Z., a 58-year-old white male, was admitted to Foundation Hospital in New Orleans on August 2, 1948, complaining that he was afraid to eat because of pain. The illness began with constipation appearing six months previously, followed by weakness, fatigue, nervousness and backache, with a 37-lb. weight loss. Three months prior to admission, dyspnea on exertion appeared. A few weeks before admission pain of two varieties appeared and became increasingly severe. One was an abdominal pain coming on two hours after eating and relieved by the ingestion of food. The other

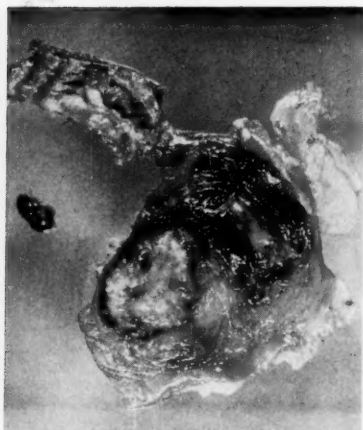


Fig. 3, Case 1.—Operative specimen of double carcinoma. Epidermoid carcinoma of the midthoracic esophagus and adenocarcinoma of the distal portion of the stomach.

was a substernal pain associated with swallowing. Anorexia and nausea also appeared and one severe bout of melena.

Physical examination revealed obvious evidence of weight loss, a right ventral hernia, and a right rectus incision for cholecystectomy. Numerous premature contractions of the heart were noted. There was no abdominal mass. The abdominal pain was thought to be due to the large ventral hernia. Laboratory findings were as follows: Hemoglobin, 9.9 gm; red blood cell count, 4.1 million; white blood cell count, 10,700; urine normal; Kline and Kolmer's tests negative; blood urea nitrogen, 19 mg%.

Fluoroscopy showed a 2.5-cm irregular lesion in the midportion of the esophagus. The stomach was reported as negative (Fig. 2). Esophagoscopy was done elsewhere with positive biopsy: squamous cell carcinoma, Grade II.

The patient was prepared for operation with three liters of blood and the administration of antibiotics, and the operation was performed on August 11, 1948. Carcinoma of the midesophagus was found (squamous cell, Grade III or IV), as well as a separate carcinoma of the stomach (distal portion) (adenocarcinoma, Grade II or III) (Fig. 3). The esophageal lesion was dissected out and then the gastric lesion found. Both the esophagus and stomach were resected, the jejunum being anastomosed to the esophagus above the

arch of the aorta. The patient never recovered from shock post-operatively. Autopsy revealed necrosis of the jejunum, spread of cancer to mediastinal, aortic and mesenteric nodes, with metastases in the liver and direct extension of tumor to the pancreas. A tubular adenoma of the right kidney (benign) was also found.

Carcinoma of the esophagus is a devastating lesion not only because of its invasive and metastatic characteristics, but also because it produces a rapidly progressive inanition as the result of early encroachment upon the lumen of the esophagus with consequent starvation. This is important not only because of the nutritional disturbances themselves, but also because of the effect upon the hemopoietic system. Lyons and Mayerson¹⁴ have shown that in individuals with chronic illnesses, such as infections or neoplasms, particularly if there is loss of weight, contraction of the blood volume is likely and if unrecognized and uncorrected, the risk of an operative procedure is greatly increased.

In addition to producing early encroachment upon the lumen of the esophagus, malignant disease of this viscus not only extends intramurally and beneath the mucosa for great distances, but also to adjacent structures within the mediastinum and is likely to metastasize to the regional lymph nodes. Because of the close proximity of the esophagus to important, vital mediastinal structures such as the trachea, the aorta, the pericardium, and the vena cava, unless an early diagnosis is made before involvement of these structures has occurred, resection is likely not to be possible.

There is probably no group of physicians upon whom a greater responsibility rests for making an early diagnosis of esophageal lesions than otolaryngologists and esophagoscopists. Since dysphagia is a prominent manifestation in esophageal lesions, particularly malignant ones, these patients are frequently referred to the esophagoscopist or otolaryngologist early in the course of the illness. Unfortunately, there are too many patients who do not come under the care of a skilled esophagoscopist early enough, because esophagoscopy remains the best method of making a positive diagnosis of primary carcinoma of the esophagus.

Incidence. Carcinoma of the esophagus is primarily a disease of males. In our series of 224 cases, 185 (75.8%) were in males and 59 (24.2%) were in females. Of the 244 cases, 173 were seen at the Charity Hospital, an institution to which both white and negro races are admitted with about equal frequency. Of this group, 98 (56.6%) were negroes and 75 (43.4%) were whites.

Carcinoma of the esophagus as in carcinoma of other viscera is primarily a disease of advancing age. In the present series, the greatest age incidences were in the sixth and seventh decades, only 4% were in individuals younger than 40 years of age, and 16% were older than 70.

Etiology. The etiology of esophageal carcinoma is not known. It is probable that chronic irritation due to ingestion of extremely hot or irritating food may be a factor responsible for the development of a malignant lesion in the esophagus. The higher incidence of esophageal carcinoma among orientals, particularly the Chinese, is thought to be due to the irritative effect of the ingestion of large amounts of extremely hot tea. Undoubtedly the presence of gastric cell rests in the lower end of the esophagus is a factor in the development of malignancy in this region since gastric mucosa is particularly susceptible to malignant change. The fact that many adenocarcinomas occur in the esophagus at some distance from the stomach indicates that these tumors undoubtedly originate in islands of gastric cell rest. Squamous cell carcinoma arises from the squamous epithelial lining of the esophagus and can be found in almost any portion of the esophagus. It is usually ulcerative and shows a tendency for proliferative growth near its borders and submucosal extension beyond its apparent peripheral limits. Because of the great tendency for this lesion to extend for considerable distances submucosally, it is imperative in performing an esophagectomy that wide resection should be done in order to insure adequate removal of the entire lesion. Adenocarcinoma is usually located in the lower portion of the esophagus and may either originate in the stomach and extend upward to involve the esophagus or it may originate, as previously mentioned, in congenital rests of aberrant gastric mucosa, which occur more frequently in the lower esophagus than in other portions. In our series, as in other series, the epidermoid or squamous cell carcinoma was the most frequent type. One hundred and thirty-eight (56.6%) were epidermoid, 42 (17.2%) were adenocarcinoma, and 12 (4.9%) were undifferentiated. In the remaining 52 (21.3%) the histologic type of tumor was not determined. Of the 192 cases in which the histologic type was determined the incidence of epidermoid carcinoma was 71.9%, adenocarcinoma 21.9%, and undifferentiated carcinoma 6.2%.

As mentioned previously, extension to adjacent viscera occurs relatively early. Of great importance also from the standpoint of curability is lymph node metastasis. Whereas lesions of the mid-portion of the esophagus are likely to metastasize to the pulmonary hilar lymph nodes, they may metastasize to the pericardiac nodes

and even to the nodes in the lesser omentum or the peripancreatic nodes. Involvement of the last nodes occurs much earlier and is more frequent in the lesions of the lower part of the esophagus, i.e., the cardia. Metastasis to the liver is also possible, particularly in adenocarcinoma in which the extension is presumably through the portal system.

Clinical Manifestations. The early symptoms in esophageal carcinoma are vague and indistinct. Although dysphagia is the most commonly encountered symptom, it is not always the first symptom experienced. In our series of cases, a little less than 65% of the patients had dysphagia as their initial symptom, although it was a symptom in approximately 94% of patients and was the chief symptom on admission in 83%. Other initial symptoms were vomiting and regurgitation, 4.9%; substernal pain, 3.7%; epigastric pain, 3.7%; and indigestion, 2.9%. In addition to dysphagia the other symptoms in order of their frequency were weight loss, 90.9%; regurgitation or vomiting, 77%; weakness, 63.5%; chest pain, 32.4%; anorexia, 30.7%; epigastric pain, 18.4%,

The dysphagia at the time of admission to the hospital was present to solids alone in 61.6%. There was dysphagia on swallowing water, but an incomplete obstruction, in 23.8%. Total inability to swallow occurred in 13.9%. In 9 cases (3.7%) dysphagia was absent at the time of admission to the hospital.

Symptoms referable to the respiratory tract may be the first noted particularly in lesions involving the cervical portion of the esophagus. McCrae¹⁷ as early as 1908 emphasized that dyspnea might be the initial symptom even before dysphagia, particularly in the presence of recurrent laryngeal nerve paralysis, which is a complication of an advanced lesion. Jackson and Jackson¹¹ stressed the importance of aspiration of ingested material into the trachea and bronchi with the production of respiratory symptoms in esophageal lesions. Camiel and Loewe,² in 13 cases with cervical esophageal involvement, observed, during the initial fluoroscopic examination of the esophagus, overflowing of barium from the pharynx into the larynx in 8. Later all except one (92.3%) showed evidence of bronchopneumonia which justified the contention by Camiel and Loewe that all had aspirated food at some time. All were advanced cases, however, and probably represented terminal lesions because 11 of the 12 cases in which the vocal cords were described had either unilateral or bilateral paralysis. In contrast to these lesions involving the upper portion of the esophagus the incidence of aspiration in lesions of the lower esophagus was unusual. Of 17 cases there were only 2 cases with aspiration, and 1 of these had a fistula. Of our 244

patients only 24, 4 of which had it as an initial symptom, complained of a cough and interestingly enough none of the 12 patients with cervical involvement had this symptom. Of the 27 with involvement of the upper third of the esophagus, 9 complained of cough, 1 of which had a fistula and of the 104 with involvement of the middle third only 9 had a cough, 3 of which had a fistula. Although probably of relatively infrequent early occurrence in esophageal lesions persistent cough demands investigation and the examination must include fluoroscopic observation of the passage of barium from the pharynx into the esophagus.

The early symptoms of esophageal carcinoma consist of vague sensation of oppression or fullness in the thoracic or substernal areas, epigastric distress, heartburn, increased salivation usually associated with ingestion of food and frequently disappearing after a meal. Such symptoms occurring in an individual, particularly a male past 40 years of age, should be suggestive of an esophageal lesion and make mandatory an investigation of the esophagus to exclude an early malignancy. Salivation is a symptom commonly found in all esophageal lesions and frequently occurs before there is any obstruction to the lumen of the esophagus. After several months of vague complaints, the symptoms become progressive and definite dysphagia appears, which is usually due to a narrowing of the lumen of the esophagus. Dysphagia in esophageal carcinoma is characteristically progressive in that in the beginning there is difficulty in eating large pieces of solid food, such as meat, but as time passes there is progressive difficulty in eating first smaller particles of solid food, then soft foods, and finally liquids.

The progress in esophageal carcinoma is usually much more rapid than in carcinomas involving other viscera. Slightly less than half of our patients (44.7%) had symptoms less than three months, 29.9% had symptoms from four to seven months. Ten and two-tenths per cent had symptoms from 8 to 11 months, 8.2% from 12 to 23 months, and 4% had symptoms over two years. The fact that one-fourth of the patients had symptoms longer than eight months is indicative of the delay which frequently occurs in these cases.

The importance of the early interference with the nutritional status of patients with cancer of the esophagus is illustrated by our findings. Only 2.7% of our patients had no weight loss, 27.9% lost 31-100 lb.; 22.1%, 21-30 lb.; 12.4%, 11-20 lb., and 9.7%, 5-10 lb.

A relatively high-grade anemia is likely to accompany esophageal carcinoma. Of 149 cases the hemoglobin estimated in grams

per cent was less than 9.7 in 17.4%, between 9.8 and 11.7, indicating a moderate anemia, in 51.7%, and 12.8 or higher in 30.9%. Similarly, the hematocrit was altered in a large percentage of cases. It was less than 42 in 80%, 32 or less in 35%, and 33-42 in 45.6%. Because of the nutritional disturbance there was a depletion of plasma protein concentrations in over half the patients. Forty-six per cent had plasma protein values of 6.8% or above; 43.8% had values of 5.8-6.7, and 10% had values of less than 5.7. The clinical picture of these patients, as typified by weight loss, provides a much truer picture of their profound debility than is obtained from these qualitative blood studies.

Diagnosis. Although frequently a diagnosis of carcinoma of the esophagus is made late, the delay is unnecessary, because there are few areas in which lesions can be diagnosed with such accuracy as in the esophagus. The esophagus lends itself exceptionally well not only to indirect visualization by means of roentgenography following ingestion of contrast substances but also to direct visualization by esophagoscopy. Roentgenography, because of its simplicity, can be done without danger unless there is complete obstruction in which there is some danger of aspiration. By means of fluoroscopic observation of the passage of a contrast substance through the esophagus, the roentgenologist can determine changes in contour, alterations in the outlines of the esophageal mucosa, and evidence of obstruction. Frequently he is able to predict the type of lesion involving the esophagus. On the other hand, esophagoscopy is more valuable than roentgen examination as a diagnostic procedure, because it not only permits direct visualization of the lesion but generally permits removal of a piece of tissue for microscopic examination. If no obvious lesion which can be biopsied is seen on esophagoscopy, the esophageal secretion should be aspirated and carefully examined for malignant cells.

A correct diagnosis was made by roentgenography in 83.8% of our 244 cases of proved esophageal carcinoma. The findings were negative in 2.8%, the diagnosis was in error in an additional 0.8%, and there was an error in designating the level of the lesion in 0.8%. Unfortunately, an esophagoscopy was not done in 18.4%. In the 199 cases in which esophagoscopy was done a positive biopsy was obtained in 160 (80%). In the remaining 39 there was suggestive evidence of tumor of which in 35 the evidence was strongly suggestive and in 4 it was only slightly suggestive. Of this group, 33 had a negative biopsy and in 6 no biopsy was taken. It is thus evident that the roentgenologic and esophagoscopic examinations gave the same incidence of correct diagnosis in esophageal carcinoma

but the fact that in 80% of the patients subjected to esophagoscopy a positive histologic diagnosis was made demonstrates the value of this method of diagnosis.

The difficulties and dangers of esophagoscopy need not be emphasized to esophagoscopists. The fact that in a series of 199 patients, perforation resulted in 3, the procedure was unsuccessful in 2, there was an error in determining the level of the lesion in 5, and an error of diagnosis in 2 emphasizes the importance of exercising extreme care in performing an esophagoscopy in patients with a suspected malignant lesion of the esophagus.

Therapy. The treatment of esophageal carcinoma may be divided into two groups, curative and palliative. There is only one curative treatment of esophageal carcinoma which consists of radical surgical extirpation of the lesion. In cases inoperable because of extension beyond the esophagus precluding the complete removal of the tumor in its entire extent, palliative resection is justified as well as other palliative procedures such as x-ray. These are not cures, however. In a series of 297 cases reported by Nathanson and Welch²⁶ it was found that the median life expectancy of untreated patients with esophageal carcinoma was seven months, of those treated by gastrostomy it was 10.4 months, and of those treated by irradiation 9.3 months. Watson³⁰ reported that the average life expectancies in cases treated by gastrostomy and external irradiation, gastrostomy and internal irradiation, and gastrostomy and internal or external irradiation were 6.3, 3.7, and 3.9 months, respectively. Zuppinger³³ found that the difference in the survival periods in those treated and those not treated was 0.3 months. According to Cleminson and Monkhouse⁵ the average survival period following irradiation is 5.6 months.

Although as mentioned above, Torek²⁸ obtained a cure in his patient by transthoracic esophagectomy, the patient, because of the persistence of cervical esophagostomy and the gastrostomy, was unable to swallow normally. With the introduction of the newer technical methods originally advocated by Adams and Phemister¹ a re-establishment of the continuity of the digestive tube has been made possible. It has been demonstrated that the stomach can be mobilized sufficiently to bring it well up into the neck and even to attach it to the pharynx, obviating the necessity in many instances of doing plastic procedures in the cervical region following the removal of a cervical esophagus. The feasibility of bringing the stomach into the upper cervical region is demonstrated by the following case.



Fig. 4, Case 2.—Pre-operative oblique view of carcinoma of the upper thoracic esophagus during barium study.

REPORT OF A CASE

CASE 2.—J. S., a 58-year-old negro male, was admitted to Charity Hospital in New Orleans on December 29, 1948, complaining of dysphagia of one year's duration. The patient was well until about December, 1947, when he first noticed difficulty in swallowing solid food particles. This was at first intermittent but then became constant and progressive. Swallowing was associated with retrosternal pain. Weakness and a 20-lb. weight loss ensued. The patient had always been able to swallow liquids freely. He had also had a dry nonproductive cough.

Physical examination was negative aside from the obvious evidence of weight loss. Laboratory findings were as follows: Hemoglobin, 11.0 gm; hematocrit, 44; white blood cell count, 5,160; blood urea nitrogen, 7 mg%, plasma protein, 6.5 gm; urinalysis, normal. X-ray examination: plain film of the chest revealed no abnormality. Fluoroscopy of the esophagus revealed a constant irregular filling defect at the level of the second thoracic vertebra with only moderate obstruction (Fig. 4). Esophagoscopy showed that 5 cm below the cricopharyngeal muscle there was a fungating mass

projecting into the lumen of the esophagus. The specimen taken for biopsy was reported as a squamous carcinoma, Grade III.

Pre-operatively the patient was given 2.0 liters of blood, the hematocrit rising to 50. Penicillin and sulfadiazine were also given. On January 18, 1949, after the patient was considered prepared, the operation was performed. Under intratracheal cyclopropane and ether anesthesia, an incision was made over the seventh rib, which was resected. The fourth, fifth, sixth and eighth were divided posteriorly. A tumor was found high in the thorax, intimately associated with the trachea anteriorly but was dissected free. The esophagus was then freed to the diaphragm which was incised radially. The stomach was freed to the duodenum by dividing the short gastric vessels, the greater omentum beyond the gastro-epiploic vessels, and the left gastric artery close to its origin. The stomach was brought up high in the thorax and was sutured to the parietal pleura along the aorta. The diaphragm was closed. The esophagus was divided at the cardia and the cardiac orifice inverted. The end of the esophagus was covered with a rubber dam and was passed up behind the arch of the aorta to lie in the apex of the thorax. An intercostal tube was inserted and the chest wound closed. The patient was placed on his back and an incision made along the medial border of the left sternocleidomastoid muscle extending down the left margin of the sternum to the second rib. The sternomastoid muscle was divided and the medial third of the clavicle and the medial third of the first rib were resected. The dome of the pleura was opened and it was planned to bring the stomach up through this aperture after the technique of Sweet. However, after the esophagus was delivered into the neck it was found that there was plenty of room in the old bed of the esophagus for the stomach and this proved to be a shorter distance and subjected the stomach to less angulation. The esophagus was freed well above the thyroid cartilage. Two small masses were present behind the thyroid and these were removed with the specimen. Using interrupted quilting cotton sutures, a three-layer tranverse anastomosis of the esophagus was made with the anterior surface of the stomach after several fixation sutures anchored the stomach to surrounding structures to relieve the moderate tension which was present. The esophagus was divided about 3 cm above the upper extent of the tumor, which was found to extend all the way through the wall of the esophagus. The neck wound was closed without drainage. The operation lasted nearly eight hours but the patient's condition remained excellent throughout. He was given 2 liters of blood during the operation. Post-operative convalescence was normal. The patient was out of bed on the second postoperative day. He took liquids on the eighth day



Fig. 5, Case 2.—Postoperative barium study showing anastomosis behind thyroid cartilage in carcinoma of the upper thoracic esophagus.

and a soft diet on the ninth day. A minor cervical wound infection developed but was not associated with a fistula. A small pleural effusion was aspirated on the fifth day. Fluoroscopy on the tenth day revealed a satisfactory stoma (Fig. 5). On the fourteenth day partial dysphagia appeared but the obstruction at the site of anastomosis responded readily to daily dilatations with soft rubber catheters.

Histologic examination of the organ removed at operation revealed a squamous carcinoma, Grade III, extending through the entire thickness of the esophagus (Fig. 6). The upper margin of the specimen was demonstrated to be beyond the visible limits of the tumor. No lymph node metastases were demonstrated. One of the masses removed proved to be a small parathyroid adenoma. The patient showed no clinical or laboratory evidence of hypoparathyroidism. The patient was discharged on the forty-fifth postoperative day eating a full diet without difficulty. He was seen two weeks later in the outpatient clinic complaining only of lack of appetite and mild dyspepsia. The transitory and readily corrected stricture probably could have been avoided had a larger opening been made at the esophagogastric junction as suggested in a pre-

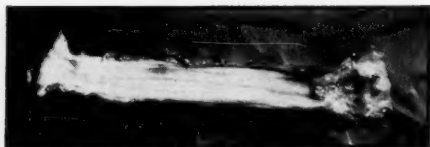


Fig. 6, Case 2.—Photograph of resected specimen in carcinoma of the upper thoracic esophagus.

vious publication.²³ In order to prevent stenosis at the anastomotic site a large opening can be made by making a longitudinal incision along the esophagus and a corresponding L-shaped incision in the stomach. In this way the size of the anastomosis is not limited by the esophageal diameter.

Because patients with esophageal carcinoma suffer from nutritional disturbances, careful pre-operative preparation is imperative before attempting surgical extirpation. As previously mentioned, failure to recognize blood volume deficiency which occurs so consistently in patients with esophageal carcinoma greatly increases the risk of the operative procedure as well as the risk of serious complications occurring postoperatively because of consequent interference with wound healing. Lyons⁴ has shown that the chronically ill patient, particularly one who has lost weight, usually has a contracted blood volume and an anemia which is not demonstrated by the ordinary blood examinations. Although the red cell count per cubic millimeter and the hemoglobin percentage may be within normal limits because of the hemoconcentration accompanying the blood volume deficiency, a severe anemia can exist. The importance of the diminished blood volume is obvious when one considers the magnitude of the operative procedure necessary and the associated operative trauma accompanying esophagectomy for carcinoma. Although a normal individual with normal blood volume might be able to withstand the same degree of trauma with little danger, an individual whose blood volume is diminished because of the debilitating condition may go into shock relatively early in the course of the procedure just as an experimental animal with an acute blood volume deficiency is unable to withstand much trauma. Uncorrected blood volume deficiency is serious not only because of the danger of the development of shock but also because of the associated uncorrected anemia which is likely to delay wound healing. As demonstrated by Whipple, in anemia there is a preferential demand upon available protein stores for the synthesis of hemoglobin. As

the plasma proteins are utilized for the synthesis of hemoglobin, in an individual with a hemoglobin deficiency, the proteins necessary for the healing of an anastomotic wound following esophagectomy may not be available and an insufficiency of the suture line is likely. We have repeatedly found in patients with esophageal carcinoma that whereas the hemoglobin percentage values may be within normal limits, i.e., 80-90%, in the same individuals total hemoglobin values are less than 40% of normal. Undoubtedly many of the earlier failures in esophageal surgery were due to interference with the normal healing at the anastomotic site because of the co-existing and usually unrecognized hemoglobin deficiency.

Although previously it was thought by many that because of the marked inanition associated with esophageal obstruction, a preliminary gastrostomy should be done to permit feeding, we have demonstrated that it is not necessary. With the liberal use of blood pre-operatively and the correction of the hemoglobin deficiency associated with the blood volume deficiency, the patient can be prepared for operation very satisfactorily. Vitamin C, because it is usually deficient in these patients and because it is essential for the healing of wounds, particularly as regards the deposition of collagen, must be administered in relatively large amounts, 500-1,000 mg daily. Because relatively few cases with esophageal carcinoma are seen before ulceration has occurred, antibiotics are administered pre-operatively in order to control not only the infection in the esophagus itself, but also to diminish the infection in regional lymph nodes. We have found that the concomitant use of penicillin, streptomycin and sulfonamides ("blitz therapy") is more efficacious than the use of any of these substances alone.

Unfortunately, surgical extirpation is not possible in a large group of cases of esophageal carcinoma because of the extent of the lesion with involvement of such vital structures as the aorta, vena cava, and trachea and also because of distant metastases. Exploration was performed in only 41.1% of our 244 cases. Before 1942, the incidence of exploration in the Charity Hospital series was only 19%. In the same institution since 1942, in 42 (38.2%) of 110 cases exploration was performed, whereas in the same period of time from 1942 to 1948, 45 (68.2%) of 66 patients seen in private practice were explored. The higher incidence of explorability in the private cases is due to the fact that these patients are seen relatively earlier than patients seeking similar care at the Charity Hospital. The fact that in the Charity Hospital series twice as many explorations were done after 1942 as were done before is significant and indicates the present philosophy of giving more of these unfortunate individuals

the advantage of at least a possible palliative resection. In the Charity Hospital series before 1942, in only 9.5% was resection performed, whereas of the 110 cases in the same institution since 1942, resection was done in 11.8%. In contrast to these are the 66 patients seen in private practice since 1942 of which 29 (43.8%) were resected.

The mortality rate in the entire group of cases is still very high. Of the 49 cases in which resection was done, 25 died in the hospital (51%). Of the cases operated upon before 1942, 85.8% died in the hospital. Of 20 cases operated upon from 1942 to 1946, there was a hospital mortality rate of 55%. In the last two years, 22 cases have been operated upon with 8 deaths (36.4%). Of the total 244 cases, in 101 (41.4%) exploration was done and of this number only in 49 (20.1% of the total and 48.5% of the explorations) was resection carried out.

A consideration of the causes of death is of interest. Five patients died of hemorrhage and shock, and an equal number died of pneumonia. In the former group only one occurred within the past 5 years, two were 5 years ago, one 7 years ago and one 11 years ago. In the latter group two occurred within the past 5 years, one was 5 years ago, one 6 years ago and one 8 years ago. Most, if not all, of these were preventable and usually can be prevented at the present time. The next most frequent cause of death was heart failure, occurring in three cases. This is a cause which will probably never be completely eliminated, because malignant lesions of the esophagus occur in older people in whom cardiovascular lesions are likely to occur. Other less frequent causes of death were atelectasis, 2, empyema, 2, mediastinitis, 2, aspirated mucus, 1, anesthesia, 1, peritonitis, 1, necrosis of the jejunum, 1, necrosis of the stomach, 1, diaphragmatic hernia, 1. It is gratifying that most of these occurred more than five years ago, because, with the exception of heart failure, we believe that all were preventable deaths.

Of 49 cases in which a resection of the esophagus was done, 25 died in the hospital (51%), 15 subsequently died (30.6%), 8 (16.3%) are still alive, 1 has not been followed (2.1%), although the last time she was heard of 14 months after operation (about a year ago), she was alive and well. The survival has not been as long as is to be desired. Of the 15 patients surviving the operation and leaving the hospital, but who subsequently have died, the survival rate after discharge from the hospital varied from 1.3 months to 38 months. Six lived less than six months, 5 lived from six to twelve months, no patient died between the twelfth and eighteenth month, 1 lived nineteen months, and 3 lived longer than twenty-

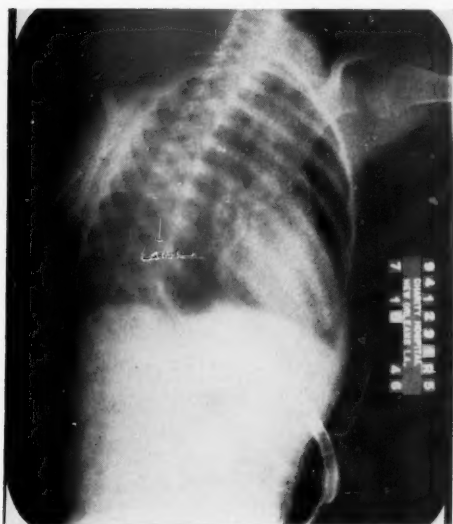


Fig. 7, Case 3.—Benign stricture of the esophagus following lye ingestion. Fluoroscopic study showing extensive stricture of lower two-thirds of thoracic esophagus.

four months. Of the 8 patients who are still alive, 2 were operated upon less than six months ago, 3 were operated from six to twelve months ago, 1, twelve months ago, and 2, more than eighteen months ago.

There are few conditions which require such careful pre-operative preparation, meticulous attention to details during the operative procedure, and constant supervision by trained personnel in the early postoperative period as do patients who have had an esophagectomy for carcinoma of the esophagus. Undoubtedly in the future, with the realization by the medical profession generally that something in a curative way can be done for carcinoma of the esophagus, earlier diagnosis will be made possible. This, together with the use of antibiotics, correction of blood volume deficiency, blood replacement during operation, and the prompt re-establishment of the normal physiologic mechanism within the thorax post-operatively will not only result in a lowering of the mortality rate, but will also give a much greater chance for permanent cure.

Benign Stricture of the Esophagus. Although it is obvious that the results obtained in the treatment of malignant disease of the



Fig. 8, Case 3.—Benign stricture of the esophagus. Postoperative fluoroscopic study after resection and primary supra-aortic esophagogastric anastomosis. No evidence of obstruction or malfunction.

esophagus are far from desirable, it must be recalled that this is a lesion that is rapidly progressing and that inoperability is likely unless an early diagnosis can be made. With time, better results can be obtained. On the other hand, the therapeutic results in the much less frequent benign strictures of the esophagus are much better. Until esophagectomy with the re-establishment of the normal continuity of the digestive tube became possible by esophagectomy and esophagogastrostomy, these patients were subjected to repeated bouginage, to a gastrostomy life, or a multistage plastic procedure consisting of an anterothoracic esophagoplasty. Although at present it is possible to excise localized segments of the esophagus and to re-establish the continuity by anastomosing the ends of the esophagus, this procedure is infrequently feasible in benign strictures because with the exception of congenital strictures which are likely to be limited in extent, most benign strictures of the esophagus follow cauterization of the esophagus as a result of ingestion of caustic substances, particularly lye. The strictures in such instances are extensive and frequently involve the entire esophagus. For this reason, localized excisions of the esophagus are usually not feasible, and

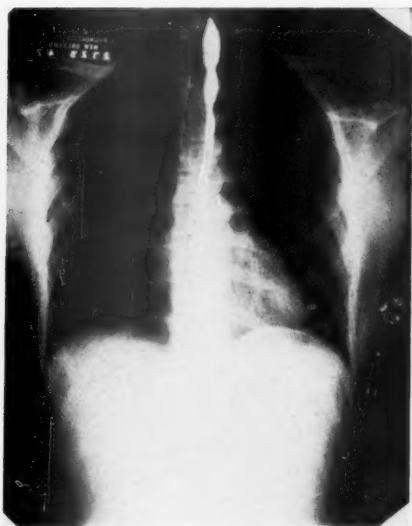


Fig. 9, Case 3.—Benign stricture of the esophagus. Lye ingestion with stricture for 30 years. Fluoroscopy showing extensive stricture of thoracic esophagus.

it is generally necessary to excise long lengths of the esophagus and frequently the entire esophagus.

Our experience in the treatment of benign stricture of the esophagus following ingestion of caustic substances is limited to four patients, all of whom have had excellent results following extensive resections of the esophagus and esophagogastrostomy. In all, repeated bouginage had been tried and had been found to be unsuccessful. The ages varied from three years to 32 years; one was three, one was four, one was 18, and one was 32.

CASE 3.—R. M., a negress aged four, ingested lye in April, 1946. She was treated elsewhere. Five weeks after the cauterization, a gastrostomy was performed and the patient was admitted to the Charity Hospital in New Orleans on July 8, 1946. Fluoroscopy revealed a normal esophagus in its upper third, but the lower esophagus was constricted to the size of a match (Fig. 7). A string was passed, retrograde bouginage performed weekly for four months without relief; the largest dilator passed was No. 26. The child was unable to swallow at all. Because of this, esophageal resection was done on January 21, 1947. The entire distal portion of the esophagus

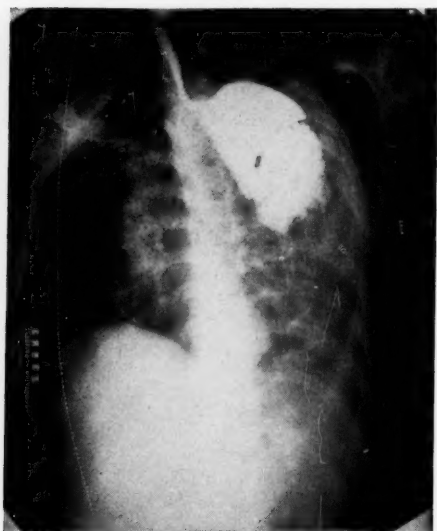


Fig. 10, Case 3.—Benign stricture of the esophagus. Postoperative barium study after resection and primary anastomosis revealing a well functioning esophagogastric stoma in the apex of the thorax.

was resected, and supra-aortic esophagogastrostomy was done through the left pleural cavity. Postoperative course was complicated by atelectasis of the left lower lobe on the first postoperative day. Following this the child got along very well and has been able to swallow without any difficulty since (Fig. 8).

CASE 4.—R. B., a white male aged 32, was admitted to the Foundation Hospital in New Orleans on February 25, 1947. The patient swallowed lye at the age of two and subsequently developed difficulty in swallowing. He was treated repeatedly by esophagoscopy and bouginage, having been esophagoscoped 107 times. At the age of 12, a gastrostomy was done, but was later allowed to close. The patient was thin, but otherwise was apparently healthy. Fluoroscopy showed smooth narrowing of the esophagus over a distance of 8 cm from the level of the anterior end of the sternum to T6, the diameter about 5 mm (Fig. 9). Esophagoscopy showed a dense 3-in. stricture at the suprasternal notch with a proximal dilatation. On March 6, 1947, an operation was performed, an esophagectomy and L-anastomosis at the apex of the thorax. The patient was given liquids on the third day, soft foods on the seventh, and a full diet

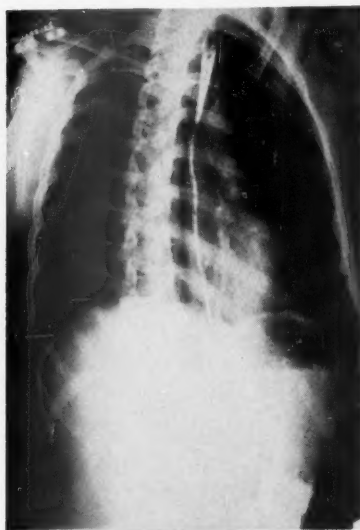


Fig. 11, Case 6.—Benign stricture of the esophagus following the ingestion of "Draino." Barium study reveals marked stricture of entire esophagus.

on the eighth postoperative day. He was discharged from the hospital on the twelfth day following an uncomplicated course. The patient states that he has some indigestion and a mild retromammary pain, but is able to swallow normally (Fig. 10).

CASE 5.—M. B., a negress aged three, was admitted to the Charity Hospital on May 18, 1948, with a chief complaint of dysphagia for five months. She had swallowed lye in October, 1947, dysphagia began in December, 1947, and a gastrostomy was performed in January, 1948. The patient was able to swallow liquids until April when complete obstruction developed. In May, 1948, an esophagoscopy revealed a stricture just below the cricopharyngeus muscle. Retrograde visualization suggested only a short stricture. Operation was performed on July 17, 1948. Resection of the esophagus was performed to above the stricture found at T7. An esophagogastric anastomosis was done below the arch of the aorta. Subsequent fluoroscopy revealed pooling of barium at T2, but with the barium entering the stomach. The anastomosis was considered to be adequate. The child is swallowing normally.

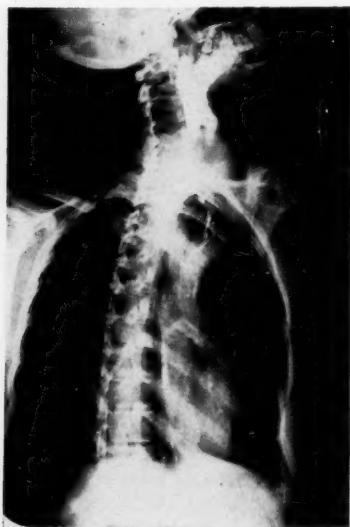


Fig. 12, Case 6.—Benign stricture of the esophagus. Resection of the esophagus with primary high cervical esophagogastric anastomosis. Postoperative fistula and stricture. Roentgen study reveals high level of anastomosis and presence of obstruction.

CASE 6.—B. J. B., a white female aged 18, was admitted to the Foundation Hospital on September 20, 1948, with the story of having imbibed Drano two weeks before in a suicidal attempt. The chief complaint was of substernal pain with dysphagia for one week. Esophagoscopy and bouginage were performed and a feeding tube inserted. Perforation of the esophagus occurred and jejunostomy was performed. The patient developed mediastinitis which was controlled by antibiotic therapy without drainage. The patient was maintained on jejunostomy feeding for three months. A diffuse stricture involving the entire esophagus developed (Fig. 11). In December, 1948, resection of the esophagus with a high cervical anastomosis was done. The stomach was brought up through the left thorax and anastomosed to the upper cervical esophagus. A fistula developed postoperatively and a stricture occurred at the site of anastomosis (Fig. 12). In March, 1949, the stenotic area was excised, and it was possible to mobilize the stomach for a considerably higher distance and to anastomose the stomach to the pharynx. Aside from a slight fistula which was temporary, the wound healed and the patient was able to eat normally (Fig. 13).



Fig. 13, Case 6.—Benign stricture of the esophagus. Revision of cervical esophagogastric anastomosis with anastomosis between the stomach and the hypopharynx. Patient is swallowing normally and barium passes freely into the stomach. Anastomosis is at the upper extremity of the roentgenogram.

Undoubtedly, in this instance the inability to bring the stomach high enough at the first operation necessitated making an anastomosis at an area with considerable residual fibrosis as a result of the cauterization. It is of interest that although the stomach could apparently not be brought any higher at the original operation, at the subsequent operation performed three months later it was possible to mobilize the stomach sufficiently well to permit resection of all of the diseased esophagus and to perform a satisfactory anastomosis. This suggests that in high-lying lesions it might be possible to perform the esophagogastrostomy in stages, permitting sufficient elongation to occur between stages to bring the stomach subsequently to a higher level.

Achalasia. The above discussed conditions, carcinoma and benign stricture of the esophagus, are organic lesions. An important functional lesion of the esophagus which is of particular interest to esophagoscopists and otolaryngologists, as well as thoracic surgeons, is achalasia or cardiospasm. Although there is considerable controversy concerning the exact mechanism of the production of this

lesion, the fact remains that there occurs in the distal esophagus a constriction which is unquestionably on a functional basis. In contradistinction to organic lesions in which dilatation of the esophagus proximal to the site of obstruction is minimal, the dilatation in achalasia or cardiospasm is massive and is associated with an elongation of the esophagus with the production of a true megaesophagus. Frequently the esophagus becomes so elongated that a sigmoid flexure of the esophagus develops. According to Walton²⁰ achalasia comprises about 17% of esophageal lesions. It is, however, the most common lesion producing symptoms referable to the esophagus in young people. It occurs primarily in neurotic young women, and undoubtedly its origin is on a functional basis. The symptoms of achalasia are those of recurrent obstruction with frequent exacerbation which are likely to be precipitated by emotional upsets. The symptoms usually date back for several years. Of 12 patients which we operated upon, only 25% had symptoms less than 1 year; 33.3%, 3-10 years; 8.3%, 11-20 years; 16.7%, 21-30 years, and in one case each there had been symptoms 33 and 55 years respectively. Because of the functional character of achalasia, psychotherapy is extremely important in its treatment and in most instances relief can be obtained by conservative measures with repeated dilatation either by means of a weighted bougie or by hydrostatic or pneumatic dilators.

Although we believe that conservative therapy should be used initially in most cases of achalasia, it must be emphasized that approximately 25% of cases do not respond sufficiently to conservative measures to justify their continuation. Until operations on the esophagus became relatively safe procedures, conservative therapy was used almost exclusively, but now one is not justified in subjecting these patients to prolonged conservative therapy when a cure can be obtained in a relatively simple and safe way. If conservative therapy is continued, complications resulting from esophagitis are likely to occur and even death may result from a complicating mediastinitis. There has been an erroneous impression that surgical therapy of achalasia entails a considerably greater risk than conservative therapy. Actually the mortality rate of the former is about the same as the latter. Moersch¹⁹ reported a mortality rate of 2.8% in 804 patients with achalasia treated conservatively, whereas in 239 collected cases in which cardioplasty and esophagogastrectomy were performed, we found that the mortality rate was 4.2%.²¹ The mortality rate of 4.2% obtained in the collected cases undoubtedly represents an excessively high figure, because most of these cases were operated upon before the newer techniques and the uses of antibiotics were available. This contention is substantiated by the fact that none of our 12 patients with achalasia operated upon died.

Because achalasia undoubtedly begins as a functional lesion, it has been suggested that attacking the nerve supply either by interfering with the sympathetic or parasympathetic supply might be of value. In 1911, Meyer¹⁸ performed vagotomy in addition to esophagoplication, but he was unable to obtain good results and this has been the experience of others. There has been only one satisfactory result in 11 collected cases in which vagotomy was performed, as originally reported by us. Recalde²⁶ was probably the first to attack the sympathetic supply to the esophagus. In 1924 he reported good results in three cases in which decortication of Auerbach's plexus was performed. Knight¹³ reported five patients in whom sympathectomy was done by excision of the left gastric artery and the surrounding fat and nervous tissue. He reported complete relief in one, considerable improvement in one, and recurrence in three. Results obtained following sympathectomy by others have been extremely unsatisfactory, and operations on the nerve supply to the esophagus have been largely abandoned.

Although many procedures have been advocated for the curative relief of achalasia, unquestionably the plastic procedures or anastomoses at the esophagogastric junction offer the best prognosis. Gottstein⁷ first proposed an extramucous cardiomyotomy, because he believed that there was a true spasm of the cardiac sphincter, but the operation was not actually performed until 12 years later by Heller.⁸ In a series of cases which we previously collected, in 104 extramucous cardiomyotomy was done. The results were reported as good in 76.9%, improved in 5.4%, recurrences in 13.4% and a mortality rate of 3.8%.

Another plastic procedure on the esophagus which is similar to pyloroplasty consists of longitudinal incision through the entire wall of the cardia and transverse closure. This was first suggested by Marwedel¹⁶ but was performed seven years later by Wendel.³¹ In our previous publication we were able to collect 36 cases in which cardioplasty was done. Good results were reported in 93%, recurrences in 2.8%, and a mortality rate of 2.8%.

The operation which we prefer is esophagogastrostomy. This consists either of a longitudinal incision in the esophagus and the adjacent portion of the fundus of the stomach or a curved incision beginning in the esophagus extending through the cardia and on to the adjacent portion of the stomach. In both an anastomosis is made between the dilated esophagus and the stomach. In the former, the cardiac orifice is short-circuited, whereas in the latter the procedure is similar to a Finney gastroduodenostomy. Heyrovsky,⁹ in 1912, originally advocated esophagogastrostomy with an incision

through the esophagus into the stomach. We have collected a total of 157 cases in which this procedure was done.²⁴ Good results were obtained in 95.5% of the patients, 3.1% died, and 1.2% had poor results.

Esophagogastrostomy for cardiospasm can be done either trans-thoracically or transabdominally. In those cases in which there is marked elongation of the esophagus which is usually present in true achalasia, it is our belief that the operation can be performed best transabdominally. By the mobilization of the esophagus one can secure a length of 12-15 cm of the esophagus in the abdomen which permits the performance of an anastomosis between the dilated esophagus and the stomach without any difficulty. The procedure is greatly facilitated by division of the left lateral hepatic ligament to permit retraction of the left lobe of the liver. In those cases, however, in which the esophagus is not elongated it is easier and, therefore, better to perform the operation above the diaphragm.

The advocates of cardiomyotomy, particularly Wooler³² and Maingot¹⁵ prefer cardiomyotomy to esophagogastrostomy because of the theoretical danger of regurgitation of gastric contents, particularly when the patient is lying down. That such a complication is possible must be considered. On the other hand, this has not been our experience. We have had 12 patients with achalasia who have been operated upon. All of these were patients who had been treated for long periods of time up to as long as 55 years with repeated bouginage which was unsuccessful in bringing about a cure. Nine of the 12 had esophagogastrostomies done, 7 of which were done transabdominally and 2 transthoracically. Three had cardioplasty. None died and all remained free from symptoms except one patient in whom a cardioplasty was done and who developed an ulcer of the esophagus just above the cardiomyotomy. In none of the patients with esophagogastrostomy has there been any evidence of difficulty from regurgitation of gastric contents into the esophagus. The follow-up period varies from two months to ten and one-half years.

On the basis of our experience and from an evaluation of the reported cases we believe that esophagogastrostomy is the operation of choice in those cases of achalasia which do not respond relatively quickly to conservative therapy consisting of psychotherapy and dilatation and in which some type of surgical relief is indicated.

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CIV

RECENT ADVANCES IN BRONCHOLOGY AND IN THE DIAGNOSIS AND TREATMENT OF PULMONARY DISEASE

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A discussion of recent advances in the field of bronchology and in the diagnosis and treatment of pulmonary disease is a formidable undertaking. The progress that has been made on this frontier in recent years comprises one of the outstanding accomplishments in medicine. Time will not permit recognition of many important contributions. In reviewing the subject, however, the fact is impressive that some of the prominent so-called new diagnostic and therapeutic procedures are actually not new, but were described many years ago; unfortunately their true value was not recognized until recently.

It is gratifying to note that understanding has increased on the part of the medical profession and the laity of the importance and value of bronchoscopy in the study of pulmonary disease. Today, bronchoscopy is accepted as a necessary and valuable diagnostic procedure. Many new instruments and gadgets have been developed in the past few years to assist the bronchologist in his work. From a teaching standpoint, a satisfactory bronchoscopic motion picture camera by Brubaker and Holinger,¹ which permits an accurate recording of changes that occur within the tracheobronchial tree, has been the outstanding accomplishment.

Middle Lobe Syndrome. One of the most interesting recent developments in the field of thoracic disease has been the identification of the condition to which the term "middle lobe syndrome" has been applied. Middle lobe syndrome consists of an obstructive pneumonitis with associated suppuration of nontuberculous origin. Middle lobe syndrome may occur at any period in life. Cough is the commonest symptom and usually the first. Patients frequently suffer from recurrent episodes of fever and hemoptysis. In its in-

Read before a combined meeting of the American Broncho-Esophogological Association and the American Laryngological, Rhinological and Otolological Society, Chicago, Illinois, April 19, 1949.

ception, the condition often is confused with pneumonia, and if it first occurs late in life, it is often regarded as carcinomatous in origin. Roentgenographic examination of the thorax uniformly reveals an atelectasis which involves the middle lobe.

Bronchoscopy is of paramount importance in the diagnosis of middle lobe syndrome. Invariably a constriction of the middle lobe bronchus will be found and, if the patient is examined when he is suffering from a superimposed infection, the mucosa will be edematous and congested and will bleed easily on the least manipulation of the bronchoscope. Frequently, purulent secretion will ooze through the mucosa at the site of the stricture. Touching the strictured bronchus with an aspirating tube or forceps gives the impression that an extraluminal mass is producing the narrowing. In one case I found a polypoid mass projecting through the stenosed portion of the middle lobe bronchus. While this mass was being observed, it suddenly disappeared beyond the stricture. Subsequently, the middle lobe was removed, and on examination a small calcified mass was found lying free in the middle lobe bronchus. The mass could be moved back and forth in the dilated bronchiectatic bronchus but was of such size that it could be only partially pushed through the stricture at the opening of the middle lobe. Bronchography invariably will confirm the presence of a stricture involving the middle lobe bronchus.

It is interesting to speculate on the etiology of middle lobe syndrome. The theory propounded by Brock² and emphasized by Graham and his associates³ seems most logical: that the condition is due to a compression of a bronchus by enlarged lymph nodes which lie in close proximity to the origin of the middle lobe bronchus. The middle lobe bronchus lies at the apex of the lymphatic pathways from both the upper and lower lobes, and is, therefore, peculiarly vulnerable to pressure from any enlargement or inflammation of these nodes. It is also conceivable that stricture may result from localized inflammation involving the bronchus.

Treatment of the middle lobe syndrome is primarily surgical and consists of lobectomy. Occasionally, a patient with middle lobe syndrome will recover from the initial episode of pulmonary difficulty and remain symptom-free for many years.

Asthma. From a bronchoscopic standpoint, obstruction of the middle lobe bronchus in middle lobe syndrome is similar to broncho-stenosis associated with asthma. It has been known for many years that patients who suffer from both allergic and infectious asthma are at times relieved by bronchoscopic aspiration of secretions but that at best this relief is only temporary. In 1940, Prickman and

I⁴ noted that not infrequently stenosis of the superior division of the bronchus to a lower lobe was encountered, and that these patients frequently gave a history of attacks of nonproductive coughing which were associated with febrile episodes either with or without preceding chills. As a rule the fever lasted two to five days. As the fever subsided, there was generally an increase in the amount of sputum expectorated. Fifty per cent of these patients gave a history of pneumonia. If the stenosed bronchus was dilated thoroughly, the patients usually experienced prompt improvement in their asthma and might remain free of symptoms for a considerable period. That the superior division of the bronchus to the lower lobe should especially be involved is not surprising as the origin of this bronchus lies in close proximity to the nodes that drain both the upper and lower lobes, and any enlargement of these nodes might readily impinge on this bronchus.

Bronchostenosis also may result from localized inflammatory processes which involve the bronchial tree. Stenosis may occur at any point in the bronchial tree and may lead to distressing and disabling pulmonary difficulty. Often the strictured bronchus can be readily dilated with forceps or dilators with amelioration of the patient's symptoms. Relief may be transitory but it is likely to be of longer duration. At times it may be difficult or impossible to visualize a stricture of this type bronchoscopically, or the stricture may be in such a position that it cannot be adequately or permanently dilated. If the patient's symptoms are of sufficient severity, lobectomy may be indicated.

Traumatic rupture of the bronchus, a comparatively rare complication of severe, nonpenetrating trauma to the thorax, may result in bronchial stenosis if the patient survives such a catastrophe. Persistent collapse of a lung after severe injury to the thorax should cause the physician to suspect the presence of this condition. Bronchoscopy is of great aid in diagnosis. The problem of diagnosis is much more difficult if the stricture has been present for a considerable period and the history of trauma to the thorax has been overlooked.

Malignant Disease. One of the most important recent advances in the field of pulmonary disease has been the development and utilization of techniques for cytologic study of sputum and pulmonary secretion in the diagnosis of carcinoma of the lung. Although Hampeln,⁵ in 1887, first described the finding of malignant cells in the sputum and pointed out the potential value of such examination in cases of suspected carcinoma of the lung, his observation received little attention. It was not until 1928, when Papanicolaou⁶ reported

his original work on a simple method of fixing vaginal smears by which good cytologic details could be obtained, that some interest was again aroused in Hampeln's report. Even then, seven years elapsed before two Englishmen, Dudgeon and Wrigley,⁷ reported that they had utilized cellular study of sputum for the diagnosis of carcinoma of the lung and demonstrated its feasibility. They reported that they were able to make a positive diagnosis of carcinoma of the bronchus from cytologic examination of the sputum in 68% of their proved cases of carcinoma. Their report stimulated a great deal of interest and favorable reaction, especially among European observers. It must be stated, however that approximately ten more years passed before this important diagnostic aid gained recognition and acceptance in this country.

Cytologic Examination: The rationale of cytologic examination of the sputum and bronchial secretion is based on the fact that desquamation of carcinoma cells takes place from malignant tumors which have a free surface. Since most primary carcinomas of the lung communicate with the bronchus, when desquamation of carcinoma cells occurs the cells should pass into the bronchus. The normal current of the bronchial secretion is cephalad. Consequently, the carcinoma cells should appear in the bronchial secretion and sputum when such a communication exists.

The criteria employed in microscopic examination of sputum or bronchial secretion for carcinoma cells are essentially the same as those employed in microscopic examination of tissue sections except for invasion. Cytologically, not only is it possible to recognize carcinoma cells, but often it is possible to distinguish the histologic type of carcinoma.

Differences of opinion exist as to the best method of collecting material for cytologic studies. Those observers who favor sputum, in preference to bronchial secretion, for cytologic examination, emphasize that it is possible to collect samples of sputum with greater ease and frequency than would be true of bronchial secretion.

In contrast to this view are the observations of Herbut and Clerf,⁸ who advocate the examination of bronchial secretion in preference to sputum. They pointed out that in their experience fully half of their patients with bronchogenic carcinoma did not expectorate sputum until the disease had progressed to an inoperable stage. Consequently, it was not possible to obtain satisfactory sputum for cytologic study at an early stage. They also stated that when sputum is abundant, or, if saline solution is used for washing out the bronchi, the material may be so disseminated that the search for carcinoma cells becomes tedious and the results often are disappointing.

Recently, Woolner and McDonald⁹ reviewed 300 cases of carcinoma of the bronchus in which the diagnosis was based on cytologic study. They found that sputum and bronchial secretions were of about equal value in diagnosis but that the best results were to be anticipated when both methods of study were utilized.

Although cytologic study of the sputum has aided immeasurably in the early diagnosis of carcinoma of the lung, especially in cases in which lesions could not be reached with the bronchoscope, it must be pointed out that experience is still an important factor in the interpretation of cytologic study. It must be kept in mind that even in the hands of the most skillful pathologist there remains an element of error in diagnosis. Wandall¹⁰ reported that in his experience an error of 3.1% occurred. Woolner and McDonald¹¹ reported that in their study error might be anticipated in approximately 2% of cases.

Bronchoscopy: Bronchoscopy is of value not only in obtaining secretions for cytologic study but also in obtaining tissue for microscopic examination. On rare occasions the results of biopsy may be positive when results of examination of sputum and bronchial secretion prove negative. Bronchoscopy also remains a most valuable aid in the localization of tumors of the lung, which is of great importance in planning the type of operation that is to be employed.

It must be emphasized that negative results of cytologic studies and biopsies do not rule out the possibility of carcinoma of the lung. Lesions, especially those that are in the periphery of the lung and do not communicate directly with a bronchus, are likely to remain undiagnosed. Exploratory thoracotomy is advisable in those cases in which doubt exists as to the diagnosis. At the clinic a high percentage of these patients has been found to be suffering from carcinoma of the lung and it has been possible to accomplish its eradication.

Treatment: Operation, when possible, is always the best method of treatment for carcinoma of the lung. In rare instances in which surgical procedures are contraindicated, a small carcinomatous lesion of the bronchus may be controlled for a considerable period by means of fulguration, the implantation of radon seeds into the base of the tumor and roentgen therapy.

Metastatic Carcinoma: Metastatic carcinoma to the lung, when it invades a bronchus, may give rise to a clinical, roentgenologic and bronchoscopic picture identical to that seen in primary carcinoma of the bronchus. Cytologic examination of bronchial secretions or biopsy of tissues from such lesions not only will enable the path-

ologist to make a diagnosis of carcinoma, but also may afford the first inkling as to the primary site of the lesion.

Alveolar-cell Carcinoma: Recently, considerable interest has been aroused in the problem of alveolar-cell carcinoma of the lung. This type of carcinoma apparently is occurring with increasing frequency, and its recognition is of considerable importance especially from a therapeutic standpoint, as it does not as a rule fit into the same therapeutic category as bronchogenic carcinoma. Alveolar-cell carcinoma is multicentric in origin and arises in the alveolar sacs. The diagnosis is therefore dependent on cytologic examination of sputum or bronchial secretion or an exploratory thoracotomy. As a rule, the patient raises little sputum and the diagnosis can be established only by examination of bronchial smears or washings. The bronchial secretion in alveolar-cell carcinoma of the lung usually is thin and watery in character and may easily be regarded as insignificant if cytologic study is not employed. There is considerable controversy as to the classification of alveolar-cell carcinoma with other carcinomas of the lung and as to the proper method of treatment.

Adenoma and Cylindroma of the Bronchus. Cytologic studies are not of value in the diagnosis of adenoma and cylindroma of the bronchus. Bronchoscopy remains the only method by which the diagnosis of adenoma and cylindroma can be established clinically with certainty. Although the majority of adenomas arise in the main stem bronchi, they occasionally arise in a bronchus that cannot be visualized bronchoscopically. In the majority of these latter cases, however, the clinical history of the patient and roentgenographic examination of the thorax should lead the physician to suspect the possible presence of an adenoma and, as in carcinoma of the lung, when doubt exists, exploratory thoracotomy should be recommended.

Tuberculosis. A real contribution to the treatment of thoracic disease has been the development and use of antibiotics in the treatment of pulmonary tuberculosis. The introduction of these potent substances in the treatment of pulmonary tuberculosis has made bronchoscopy of even greater importance than it has been in the past.

Schatz, Bugie and Waksman,¹² in 1944, reported the isolation of streptomycin and noted that this antibiotic had a definite restraining action on cultures of *Mycobacterium tuberculosis*. The same year, Feldman and Hinshaw¹³ reported that streptomycin had a decidedly beneficial effect in experimental tuberculosis, and the following year they reported its use in clinical tuberculosis. It soon

became apparent that streptomycin was of value in treatment of certain types of tuberculosis, especially ulcerating tuberculous lesions involving the tracheobronchial tree. It proved of great value to the thoracic surgeon in those cases of pulmonary tuberculosis in which operations on the lung or thoracic cage were necessary or indicated.

It has become apparent, however, that there are certain drawbacks to the routine use of streptomycin in the treatment of pulmonary tuberculosis. It has been demonstrated that, as a rule, streptomycin can be used for a period of only two to four months at a time, as the organism of tuberculosis may become resistant to the drug. It is imperative that streptomycin be used only at the time, during the course of the disease, when the greatest benefit can be expected. The immediate benefits of streptomycin are limited as a rule to a period varying from several weeks to, at most, three months. Obviously, therefore, it is extremely important that the period of chemotherapy be worked into any over-all plan instituted for the care of the patient.

Streptomycin also may give rise to certain toxic manifestations which must always be considered in the administration of this drug. It may produce a disturbance of vestibular function; deafness may occur. Usually, partial or complete compensation will be noted in the vestibular disturbance on cessation of the use of the drug. Hearing usually will be regained after the therapy is discontinued. Serious renal damage may occur, but this is extremely rare. Cutaneous lesions are occasionally observed and, very rarely, there may be an exfoliative dermatitis.

Obviously, the first essential, if a drug such as streptomycin may be used over a long period, is to be certain of the diagnosis. Unfortunately, pulmonary tuberculosis is often protean in nature and its diagnosis difficult. When the diagnosis of tuberculosis is not certain, bronchoscopy may often be of great aid. At times, tissue may be obtained from an intrabronchial lesion which may permit the establishment of the diagnosis. Often the diagnosis can be made from culture of laryngeal smears or bronchial secretions removed at the time of bronchoscopy.

Bronchoscopy is indicated for any patient with pulmonary tuberculosis who presents a history or physical findings suggestive of bronchial obstruction. It is advisable in all cases in which results of tests of the sputum are persistently positive, even though the pulmonary lesion appears to be healing satisfactorily clinically and roentgenographically. It is indicated in all cases in which operation is to be undertaken in order to determine the presence or absence of tracheal or bronchial involvement. It is of value in the study of

tracheobronchial tuberculosis when the patient is undergoing treatment with streptomycin.

In the past year, dihydrostreptomycin has been developed and has been found to possess the beneficial effects of streptomycin with a decrease in its neurotoxicity. At present this preparation is to be preferred to streptomycin alone. Vestibular disturbance may be produced by dihydrostreptomycin, but it occurs late in the course of the treatment. As a rule this drug does not cause serious symptoms and repeated caloric tests do not reveal complete loss of labyrinthine function. Dihydrostreptomycin occasionally causes some local irritation both on intramuscular and intrathecal administration. The occurrence of drug-resistant strains in pulmonary tuberculosis is still a paramount problem in the use of dihydrostreptomycin, as the organisms which are resistant to streptomycin are also resistant to dihydrostreptomycin. It seems that some progress against this tendency is being made by combining streptomycin with promin and para-aminosalicylic acid (PAS).

Aortic Aneurysm and Congenital Anomalies. The bronchologist and the thoracic surgeon not infrequently are confronted with the problem as to whether or not a mediastinal mass, which produces deformity or invades the tracheobronchial tree, is due to an aneurysm. The dread of removing tissue for biopsy from an aneurysm or of cutting into one is something that cannot be easily dismissed, and such a procedure is a catastrophe that many have experienced. In spite of the most careful investigation, the diagnosis of aortic aneurysm has not always been possible in the past. Aortic aneurysm may mimic many mediastinal tumors and can give rise to a picture similar to that seen in carcinoma of the lung.

Angiography may be of considerable assistance in distinguishing the aortic aneurysm from other types of mediastinal lesions.

Congenital anomalies involving the cardiovascular system may compromise respiration by pressure exerted on the trachea and bronchi. Such pressure may be exerted by congenital lesions of the heart but more frequently results from anomalies involving the aorta or its branches. When such pressure occurs, it may produce stridulous breathing, cough, dyspnea and cyanosis. The symptoms are frequently accompanied by dysphagia or aggravated by deglutition. The diagnosis may be extremely difficult as roentgenograms of the thorax are frequently noninformative. Because of the symptomatology, bronchoscopy is often advised and not infrequently, as Holinger, Johnston and Zoss¹⁴ have pointed out, the first clue to the cause of the compression is derived from such an examination. Early recognition of such anomalies has become of special importance

since, as Gross¹⁵ has demonstrated, surgical interference may be successful.

Bronchogenic Cysts. Bronchoscopy should be employed in the study of all patients suffering from bronchogenic cysts. Not only is it of value in distinguishing these cysts from other intrathoracic tumors, but also it may afford the first information regarding carcinomatous changes. If not infected, bronchogenic cysts may remain asymptomatic for many years, although some that have become infected may be asymptomatic for equally long periods. Because of this, bronchogenic cysts may be regarded as harmless and their removal not advised. Actually the lining of a bronchogenic cyst is similar to bronchial mucosa and consequently there is the same chance for development of malignant change. Clagett and I¹⁶ found that in 4% of the cysts seen at the Mayo Clinic carcinomatous changes have developed. It is at times possible to identify its presence by the examination of bronchial secretions coming from the bronchus communicating with the cyst. The importance of early recognition of malignant change in a bronchogenic cyst is obvious, and prompt removal of the cyst is imperative.

Atelectasis in the Newborn. Heatley and Emerson¹⁷ recently called attention to the value of bronchoscopy in the treatment of atelectasis in the newborn. Normally, complete expansion of the lung of the newborn requires two to four days and a somewhat longer period if the infant is premature. In most cases atelectasis affects only a small portion of the lung and it is present for such a short time that it is not significant. Occasionally, however, atelectasis affects a portion of such size and is persistent to the extent that it may give rise to alarming symptoms and even death. Prompt bronchoscopic aspiration of the bronchial tree often may prevent such a catastrophe. In these cases it is sometimes difficult to decide when bronchoscopy should be instituted. One hesitates to subject a tiny infant to an unnecessary and difficult procedure and still, if one waits too long, irreparable damage may result. In general, it may be stated that if the area of atelectasis is not great and if cyanosis or dyspnea is not present, the infant may be observed for 12-24 hours without too great danger. In most cases the atelectasis will clear up spontaneously. When this does not occur, bronchoscopy should be performed. As Anspack¹⁸ and Holinger¹⁹ demonstrated, persistent atelectasis in the infant and child may be the forerunner of bronchiectasis.

Fibrocystic Disease of the Pancreas. Atkins²⁰ is of the opinion that bronchoscopy is of value in the diagnosis of fibrocystic disease of the pancreas. Fibrocystic disease of the pancreas which develops

early in infancy is characterized by absence or diminution of the pancreatic enzymes with poor utilization of the proteins, starch, fat and fat-soluble vitamins. The patients pass large, soapy, foul stools and are subject to frequent respiratory infections which may cause marked respiratory embarrassment. Atkins has concluded that fibrocystic disease of the pancreas produces a characteristic change in the tracheobronchial tree described as hyperemia of the bronchial mucosa which sometimes is granular in character. As a rule the bronchial spurs are thickened and the bronchi are obscured by the presence of extremely viscid, purulent or occasionally blood-stained mucus. Although such changes should suggest the possibility of fibrocystic disease of the pancreas, when they occur in children it is highly problematic that they are characteristic enough to establish a positive diagnosis without other confirmatory evidence.

Bronchoscopy is of considerable value in the care of patients who have fibrocystic disease of the pancreas. One of their major difficulties is that of recurrent bouts of pulmonary infection with associated respiratory embarrassment. The secretions are usually very tenacious and difficult to expectorate, and bronchoscopic aspiration may afford the patient considerable relief and may prolong life.

Intrathoracic Thyroid Tumor. The diagnosis of intrathoracic thyroid tumor, when the tumor is situated in the lower half of the anterior thoracic cage, may present an extremely difficult problem. The difficulty of diagnosis is especially great if the patient does not have an enlarged thyroid gland or a history of such an enlargement to direct curiosity in that direction. Roentgenoscopic examination of the thorax generally reveals evidence of motion of an intrathoracic goiter in the upper portion of the thorax on deglutition, but it is seldom informative of those tumors situated in the lower portion of the thorax. In the past, positive identification of tumors of this type has generally been based on surgical removal although radioactive iodine has been of value in the pre-operative identification of such tumors in certain cases.

It is only certain types of thyroid tissue that have the ability to take up and concentrate radioactive iodine. If radioactive iodine is given to a patient with an intrathoracic goiter or any tumor which contains thyroid tissue, this isotope will be concentrated in the tumor. By passing a Geiger counter over the chest of the patient, the concentration of the radioactive substance can be identified and the diagnosis of intrathoracic thyroid tumor established.

Aerosol Therapy. The use of aerosol therapy in cases of infections of the tracheobronchial tree has recently received considerable attention. The success of its use is dependent in large measure on the

proper selection of patients to be treated and on the choice of the proper type of aerosol. The bronchologist can and should be of definite assistance in these matters. Before treatment is instituted it is advisable for the patient to undergo bronchoscopy to determine, if possible, the cause of the infection or, better yet, to exclude possibilities such as an unsuspected foreign body, tumor, stricture or broncholith. Secretions should be aspirated and studied to determine the character of the infecting, or at least of the predominating infecting, organisms so that the proper antibiotic may be used.

It is not necessary to describe in detail the various methods of nebulization, but it may be of value to re-emphasize that in order to obtain the best results the aerosol to be used should be one that can be properly and uniformly distributed throughout the bronchial tree. It may be of advantage to check bronchial cultures from time to time during the course of treatment, especially if satisfactory results are not being accomplished.

Aerosol therapy may be valuable in selected cases for conditions such as bronchiectasis, bronchitis, pulmonary abscess and purulent pneumonitis.

COMMENT

In the past few years much progress has been made in the field of bronchology and in its application to the study of pulmonary disease. Its field of usefulness in the study of fungous infections of the lung has been amply covered in the literature. The possibility of establishing a diagnosis of pulmonary infections is far better from a study of cultures of bronchial secretions than from a study of samples of sputum alone. Bronchology has been of definite assistance in the study of pulmonary physiology and in the understanding of factors that may play a role in its alteration. It has been demonstrated that bronchology may often be of value in the study of pulmonary lesions of obscure origin or type such as Boeck's sarcoid, amyloid disease and pulmonary fibrosis associated with atherosclerosis. Bronchology has truly more than justified the confidence of the men who first promoted its development.

MAYO CLINIC.

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TUMORS OF THE UPPER LOBE OF THE LUNG

BRONCHOLOGIC AID IN DIAGNOSIS
AND TREATMENT

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Tumors of the upper lobes of the lung present difficulties in diagnosis not usually encountered in lower lobe tumors. The lower lobes are more readily examined bronchoscopically by the usual methods. Careful technique and the use of telescopic examination have largely overcome this difficulty. Material for examination, bacteriologic and cytologic, may now be as accurately obtained from the upper lobes as from the lower. X-ray examination by antero-posterior and lateral films and planographic studies are indispensable in definite localization of the lesion. If the diagnosis is made early in upper lobe lesions, complete surgical removal will produce a better chance for cure than in lower lobe lesions, because the lesion is well away from the hilum and direct extension and lymphatic drainage will be later than in involvement of the main and lower lobe bronchi.

I wish to present a group of cases in which the endoscopic findings were unusual.

REPORT OF CASES

CASE 1.—*Benign Tumor of the Left Upper Lobe Bronchus.* This case has been previously reported but I wish to review the endoscopic findings. A man, 57 years of age, was admitted to the Graduate Hospital of the University of Pennsylvania with fever, and on examination was found to have a localized lesion involving the lingular portion of the left upper lobe. He had been under observation for a period of three months, and on admission had a septic temperature and purulent expectoration with wheezing respiration. Bronchoscopic examination showed the pus to be coming from the left upper lobe bronchus. Visualization directly through the bronchoscope showed a mass obstructing the lower portion of

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

the left upper lobe. We were able to remove directly a specimen of tissue. A grayish, smooth, nodular mass was protruding from the bronchial orifice. Histologically it was reported as a benign, inflammatory nodule, with calcareous deposits and true bone formation. At the second bronchoscopy the mass was removed quite easily from the lower division of the left upper lobe. There was no bleeding and the dilated bronchus presented a smooth, grayish surface that resembled in appearance the inside of a chestnut burr. Removal of the obstructing mass allowed free drainage and the patient made an uneventful recovery.

The histologic examination of the tissue by Dr. E. A. Case was reported: "In the center of the mass is a piece of bone 5 x 3 mm showing cells resembling bone marrow and loose edematous material suggesting cartilage." The opinion was advanced that it was primarily an inflammatory process with bone formation. This case was observed in 1929, before the days of pneumonectomy, and it was extremely fortunate for the patient that the tumor was benign and that the bronchoscopic removal effected a cure.

CASE 2.—Fungus Infection and Primary Sarcoma of the Left Upper Lobe. An ex-G.I., 22 years of age, who had returned from service in Okinawa was admitted to the Williamsport, Pennsylvania hospital because of pulmonary disease which had existed for a period of six weeks. He was bronchoscoped and an obstructive lesion was found in the left bronchus. Tissue was removed and on examination was reported as inflammatory tissue with evidence of fungus infection. His condition did not improve and he was referred to my service at the Graduate Hospital for further examination and treatment.

On admission, x-ray examination of the chest showed a radiopacity measuring 1 in. in diameter, associated with peripheral hilar infiltration having the appearance of lymphoblastoma. Bronchoscopic examination showed a fungating mass which seemed to fill the greater portion of the upper lobe bronchial lumen. The tissue removed had the appearance of an organized fibrinous exudate. It was removed with forward grasping forceps without producing hemorrhage. A small amount of secretion was evacuated and examination of the airway to both lower and upper lobes showed the lumen to be unobstructed. The bronchial obstruction was relieved, and on a second bronchoscopy four days later, both upper and lower lobes were clear. X-ray examination showed that the mass in the periphery of the left lung was unchanged. Two weeks later a third bronchoscopy showed a whitish area about 3 mm in diameter, typical

in appearance of a mycotic infection. Pathologic examination of the material removed from the left, main and upper bronchus "shows a fungus with coarse branching structure with slight clubbing at intervals. The morphology is that of *aspergilus*." (Drs. Case and Dapena.)

Bronchoscopic examination one week later showed thick tenacious material in the left upper lobe bronchus which was readily aspirated and on retrograde telescopic examination the mucous membrane appeared red. No fungations were seen. The patient was generally very much improved and was allowed to return home but was kept under observation. X-ray studies showed that the mass in the left lung had increased in size and six weeks later he was referred back for further bronchoscopic observation. Bronchoscopic examination at this time showed the lesion to be limited to the left upper lobe. A firm, reddish mass was filling the lingular division of the left upper lobe bronchus. Adequate biopsy material, aspirated secretions, was obtained and on histologic examination was reported as a malignant tumor. "The tumor is made up of rather densely packed oval and spindle-shaped cells showing a moderate amount of variation in size and staining quality of the nuclei. There are many blood vessels throughout the tissue. Mitotic figures are numerous. Diagnosis: Sarcoma." (Drs. Case and Dapena.)

The patient was referred to Dr. Herbert Reid Hawthorne who did a pneumonectomy and the patient made an uneventful recovery. Dr. Hawthorne reported as follows: "A rounded, soft, reddish-gray mass about 4 cm in diameter protruded from the medial surface of the lingula near its outer aspect. The surface of the lesion was uniform and smooth and the mass was very soft to palpation. The tumor was sharply demarcated with no gross evidence of extension into the surrounding lung tissue. The peripheral portion of the lingula was slightly atelectatic.

"The specimen was examined grossly after removal. The tumor mass was about 4 cm in diameter and was soft in consistency. The bronchus leading into the lingula was opened and a grayish tongue of tumor tissue was found protruding into the lumen of the bronchus about 5 cm above its origin. When the bronchus was further divided the center of the tumor was entered. The cut surface was uniformly gray and somewhat shiny, resembling a solid jelly-like substance. The outer borders of the tumor were well defined and the shape was quite well rounded. The tumor tissue was well distributed around and in the area where the main bronchus to the lingula divided into its smaller branches."

CASE 3.—*Metastatic Melanoma of the Lung.* A male, 43 years of age, was admitted to Fitzgerald-Mercy Hospital December 17, 1947, because of general weakness, regurgitation of food, hoarseness and progressive loss of power in his right arm. There was also some evidence of mental impairment. X-ray examination of the chest showed a mass in the right hilum about 10 x 4 cm. Laminagraphy showed some evidence of compression of the right upper lobe bronchus. Bronchoscopy showed no abnormality down to the level of the bifurcation. Examination of the right, stem and upper lobe bronchus showed some narrowing of the bronchial lumen with an irregular nodular appearance of the mucous membrane and a film of grayish-black exudate covering the entire surface of the circumference of the mucous membrane of the upper lobe bronchus. The appearance was that of the application of black paint to the bronchial lumen. There was no definite fungation but when swabs were applied, blood-stained secretion was obtained. From this secretion and from scrapings with the ball type specimen forceps, small fragments of tissue for microscopic examination were obtained.

On physical examination small, metastatic nodules could be felt beneath the skin of the abdomen. These nodules had apparently been noticed by another physician three months earlier; he had instructed the patient to return in the fall for further examination. The smear and tissue specimens from the right upper lobe bronchus were reported as melanoma, metastatic. "The sections show small clusters and sheets of atypical cells which could be epithelial in origin but present the unusual features of small clusters of brown pigment which is iron negative with a specific stain. Diagnosis: Metastatic melanoma."

Following this report nodules were excised beneath the skin of the abdomen. These nodules gave a more typical picture of metastatic melanoma, confirming the diagnosis from the bronchoscopically removed specimen. The condition progressed rapidly and the man died at the end of two months. We were unable to obtain a post-mortem examination to determine if possible the site of the primary lesion.

CASE 4.—*Bronchogenic Carcinoma of the Left Upper Lobe.* A male, 60 years of age, was well until six months prior to admission, during which time he lost 20 lb. in weight. He exhibited marked dyspnea on exertion. There had been no cough or hemoptysis. The patient had had several x-ray check-ups over a period of years. Chest examination had shown some evidence of density in the left upper lobe which had been diagnosed as healed tuberculosis. At the time of his admission, x-ray examination showed a round

mass with a diameter of about 5 cm in the left upper lobe which had not been seen in any previous films. Bronchoscopy was performed on three occasions. Careful examination was made of the tracheobronchial tree with particular reference to the left upper lobe area. Attempts were made to obtain specimens for cytologic examination by aspiration in this area, and bronchial washings were made from the same region. No cancer cells could be found at these examinations. In spite of this negative examination we felt that the lesion was probably cancer and advised exploratory thoracotomy. An extensive carcinoma of the left upper lobe was found. The left lung was removed and there was noted some probable extension to the pleura at the apex of the lung. The man made an uneventful postoperative recovery and at the present time is receiving x-ray therapy over the left upper lobe area of the chest wall. This case illustrates the advisability of exploratory operation in round lesions in the upper lobes of the lung, as advised by Evarts Graham. If an exploratory procedure had been done previously it is quite probable that the diagnosis could have been made much earlier in this case.

CASE 5.—*Carcinoma of the Left Upper Lobe Bronchus.* A male, 47 years of age, complained of hemoptysis (a tablespoonful of blood) on September 7, 1947. He was told by the family physician that the blood came from his tonsil. X-ray films showed some thickening in the region of the left upper lobe. Examination repeated six weeks later showed roentgen evidence of increase in the mass in the left upper lobe, with atelectasis extending upward, involving the upper lobe of the left lung. The patient was admitted for diagnostic study. Bronchoscopic examination showed no evidence of ulceration in the left, main and lower lobe bronchus. Retrograde telescopic examination of the left upper lobe showed a fungating lesion blocking the lumen of the left upper lobe bronchus, typical in appearance of carcinoma. Aspiration of the secretion which was blood-stained, showed typical carcinoma cells. Pneumonectomy was done by Dr. Herbert Reid Hawthorne. The patient made an uninterrupted recovery, was up on the second postoperative day and discharged from the hospital on the eighth. At the end of three months he had resumed his occupation.

CASE 6.—*Carcinoma of the Right Upper Lobe.* A male, 52 years of age, consulted his doctor because of pain in his right upper chest which he felt was due to muscular effort occurring while at work (locomotive engineer). He was also hoarse, and mirror examination of the larynx showed redundant tissue which accounted for this. The tissue was removed by direct laryngoscopy and micro-

scopic examination proved it to be benign inflammatory tissue. Bronchoscopic examination showed a small amount of mucoid secretion in the right lung and retrograde telescopic examination showed a small fungating area on the posterior wall of the right upper lobe bronchus. Secretion was obtained from this area which was slightly blood-stained, and showed on microscopic examination no evidence of cancer cells. The appearance on retrograde telescopic examination was that of an inflammatory lesion. X-ray examination was so characteristic of tumor that exploratory thoracotomy was advised. When the chest was opened a large carcinoma was found involving the apex of the lung. The upper half of the mass on section showed typical carcinoma; the lower half was necrotic tissue and showed no carcinoma on microscopic examination. The lung was removed by Dr. Herbert Reid Hawthorne. The patient made an uneventful recovery, was out of bed on the first postoperative day, left the hospital on the eighth and went back to his work as engineer at the end of three months, having gained about 10 lb. in weight.

250 SOUTH 18TH STREET.

CVI

ADENOMA OF THE TRACHEA

HOWARD McCART, M.D. (By Invitation)

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Tumors of the trachea are rare; especially is this true of adenomata and more particularly those arising from the cervical portion of the trachea.

There has been an apparent increased incidence of carcinoma of the trachea along with bronchogenic carcinoma in the past few years, and more recently there has been noted a similar increase in benign tumors of the trachea. The diagnosis of tumors of the trachea is generally established late in the course of the disease, due to the lack of early symptoms. When the tumor mass enlarges to the extent that air can only pass in and out in limited amounts, the patient becomes conscious of progressive discomfort in breathing, i.e., dyspnea.

Swartz¹ reported an adenoma of the trachea in the extreme upper portion at the level of the second tracheal ring, which he removed by biting forceps, the tumor recurring in two years; the patient refused an external surgical removal of the growth. He was unable to find a report of a similar case in the medical literature. Harrill² reports a case of adenoma of the trachea following injury. This growth was situated at the level of the second or third tracheal ring and was removed on two occasions. Smith³ reported an adenoma of the trachea situated below the level of the right cord, which he removed successfully by an external surgical approach. He reported no evidence of a recurrence over a period of five years.

The histological and pathological aspects of adenoma of the trachea should be considered as analogous to those of bronchial adenoma. Bearing this in mind, the benign nature of adenoma of the bronchi was first recognized by Heine⁴ in 1927. He described the

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Submitted as Candidate's Thesis to the American Broncho-Esophagological Association.

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

cells as well differentiated, with no unruly growth. Reisner⁵ in 1928 reported another case. In both of these cases the tumors were found at postmortem examination.

Kramer⁶ in 1930 diagnosed the first cases of bronchial adenoma during life, 23 cases, which were successfully treated; it is interesting to note that he felt local malignancy might occur. Since this time there has been a more general recognition of adenomata situated in the bronchi, and recently, four cases of adenomata in the trachea. Wessler and Rabin⁷ emphasized the mechanical effects of such tumors, which are seen in a much later stage in tumors of the trachea.

Morlock and Pinchin,⁸ in 1935, found in a series of 150 bronchial new growths that 6% were benign. It would appear that benign growths of the trachea are even more rare. Since that time, reported cases have become more numerous⁹⁻¹⁹ and it has been shown that the pathology of adenomata is still obscure and that these tumors do not always have a highly developed glandular structure, thereby giving rise to some difficulty in diagnosis. Womack and Graham²⁰ advanced the theory that adenomata were developmental in origin, analogous to mixed salivary gland tumors. Brock²¹ and Thomas²² have also mentioned the resemblance to salivary tumors.

The rarity of adenomata of the trachea is established in that only three cases have been reported in the literature; to this is added a case report.

While four cases is too small a group to base an analysis as to sex or age, it is interesting to note that three were females and three were between 21 and 37 years of age, the fourth being 61 years.

The history of symptoms in these cases was comparatively short, distinguishing them from bronchial adenoma and carcinoma of the trachea and bronchi, in which there is a long history of symptoms. Dyspnea, increased by exertion, was the most prominent symptom in the four cases. Cyanosis was noted in two cases. Cough was present in one of the four cases of tracheal adenoma, and then only mentioned occasionally. Hemoptysis was mentioned in one case, and then only at the time of the injury; it was moderate in amount and subsided in three to four days.

The etiology is obscure; in one of the four cases, previous disease of the lung was mentioned, namely, a history of bilateral pneumonia 24 years previously, but it is of doubtful significance; however, two gave a history of repeated upper respiratory infection.

Tracheal tumors, especially of the cervical region, give rise to only one symptom, that is, dyspnea, the obstruction being of the by-pass valve type²³ and obviously infection had not been noted as

is so common in cases of adenoma of the bronchi; nor had there been noted any extratracheal extension.

Gross Appearance. These tumors, when viewed through a bronchoscope, appear pinkish in color, with no evidence of ulceration, and have a broad base. They do not appear to have any extra tracheal extension.

Diagnosis. Histological examination of tissue is the sole method of establishing the diagnosis of tracheal adenoma.

Pathology. These tumors are covered with ciliated columnar epithelium which has undergone squamous metaplasia of varying degree, resting on an intact basement membrane. The tumor cells do not invade the epithelium, showing that the growth is extensive rather than infiltrative. Beneath this epithelium there is a deep layer of loose connective tissue containing numerous thin walled blood vessels.

The tumor proper consists of masses of cells supported by a scanty stroma of vascular fibrous tissue. The tumor cells are most commonly cuboidal in shape, the cytoplasm is scanty and clear, and vacuolation of the cytoplasm is occasionally seen. The nuclei are large, uniform in size and hyperchromatic. They are round or oval in shape and rarely irregular. Nucleoli are seldom seen. Mitoses are rare. The tumor cells generally show a regular arrangement. The peripheral cells tend to stain more darkly and are scattered irregularly in columns and masses at the margin of the connective tissue layer. The cells of the tumor proper are always epithelial in type and may show some differentiation along glandular lines. The arrangement varies from highly specialized alveoli and tubules in some examples to the aggregation of cells in solid acini and anastomosing columns, or the formation of irregular parenchymatous masses; in others, mucus is occasionally seen in the glandular spaces. Although the type of cell is essentially the same in all tracheal adenomata, there may be distinct variations in the arrangement of the cells, thereby causing confusion in diagnosis. Some writers have placed so much stress on the glandular arrangement of the cells that the tendency has been to regard all tumors without this structure as carcinomatous.

Confusion will occur until it is recognized that tracheal adenomata, like bronchial adenomata, show degrees of differentiation and that a glandular arrangement is not the only criterion for identification.

The appearance of a biopsy specimen may vary according to the part of the tumor from which it is removed; damage by dia-

thermy or pinching by forceps produces distortion and tissue damage so that these atypical cells appear to infiltrate the stroma in a way simulating malignancy.

These tracheal adenomata should be considered as potentially malignant. Distant metastases have never been reported, but the presence of small areas of nuclear hyperchromatism and occasional mitoses have been reported, as well as infiltration of the bronchial wall.⁹ In other cases small submucous plaques of adenomatous tissue were seen in the bronchus above the actual growth which tends to recur on removal. The tumor cells did not invade in any case the thin walled blood vessels, nor were the lymphatics invaded.

Origin. Tracheal adenomata do not appear to originate in the tracheal epithelium, since this is always present as a continuous layer over the surface of the growth from which it is separated by an intact mucous membrane. The most probable site of origin is the secretory ducts of the tracheal glands; on the other hand, mucus sometimes is seen in section, thus it would seem that tracheal adenomata are probably tumors of the whole gland.

The similarity of tracheal and bronchial adenomata should be born in mind. Womack and Graham²⁰ feel that the latter are similar to mixed tumors of the salivary glands, that they are locally malignant, that they have a developmental origin and that they contain entodermal and mesodermal structures. However, no other writer has reported mesodermal structures present on section. The resemblance between mixed salivary tumors which locally infiltrate and adenomata of the trachea is very close, as both have a tendency to glandular formation of the duct, to acinous type, and both can exist in varying degrees of differentiation. This close similarity has also been noted by Brock²¹ and Thomas.²²

The glands of the trachea are comparable to the salivary glands developmentally, being composed of serous and mucous elements, in varying proportions and even contain crescents of Gianuzzi. Therefore it is reasonable to conclude that tracheal adenomata and mixed salivary tumors are identical in nature. The structure of each individual adenoma of the trachea, like bronchial gland tumors, tends to be uniform, thus one growth may be composed of undifferentiated elements only, while another may be entirely glandular, but it is uncommon to find both types of structure in the same tumor.

REPORT OF A CASE

M. D., an unmarried white female, aged 21, was referred by her physician because of progressive dyspnea over a period of three months. On admission to the hospital, physical examination re-

vealed a slight cyanosis. Wheezing was heard over the entire chest on auscultation. An x-ray film of the chest was negative. There was no history of cough or hemoptysis, nor was there anything significant in the history of past illnesses.

Indirect laryngoscopy showed a granular appearing mass, pinkish in color, in the right subglottic region. Because of increased dyspnea shortly after admission to hospital, a tracheotomy was performed under local anesthesia. The incision was carried upward from the level of the fourth tracheal ring to include the arch of the cricoid cartilage. The tumor was found attached by a broad base at the first tracheal ring arising from the right anterolateral wall and measured 1.5 x 1.5 cm. Following removal of the tumor with biting forceps, the base was cauterized by a coagulating current.

The patient was discharged from hospital two weeks following operation, symptom free and with no evidence of residual new growth. She was requested to return to hospital for re-examination at an interval of four weeks, which she failed to do, also ignoring a written reminder. Six months later, the patient was re-admitted to hospital because of dyspnea.

Direct laryngoscopy revealed a slight lack of movement of the right cord with a recurrence of the tumor in the right subglottic region. The old wound was re-opened and the airway re-established with a tracheotomy tube. It was found that the base of the tumor had infiltrated upward to the right cord, and had become more annular, extending medially to about 0.5 cm past the midline of the trachea at the level of the first tracheal ring. The growth was again removed and the base cauterized with a coagulating current. Because of the recurrence and extended infiltration of the tumor, it became evident that a laryngectomy was advisable. This the patient declined to have performed. The patient was discharged from hospital with the tracheotomy tube in situ. Following a period of another three months, re-examination showed that the tumor had recurred to a greater extent, as evidenced on indirect laryngoscopy and on viewing through the tracheotomy opening. There was no enlargement of the cervical glands.

The patient consented to a total laryngectomy when the growth had invaded the skin about the tracheotomy opening. At operation there was invasion of the strap muscles, and massive invasion of the thyroid gland so that it was very difficult to determine a line of demarcation between the new growth and thyroid gland. However, it was felt that enough thyroid tissue was left posteriorly so as not to remove the parathyroid glands. There was also some extension

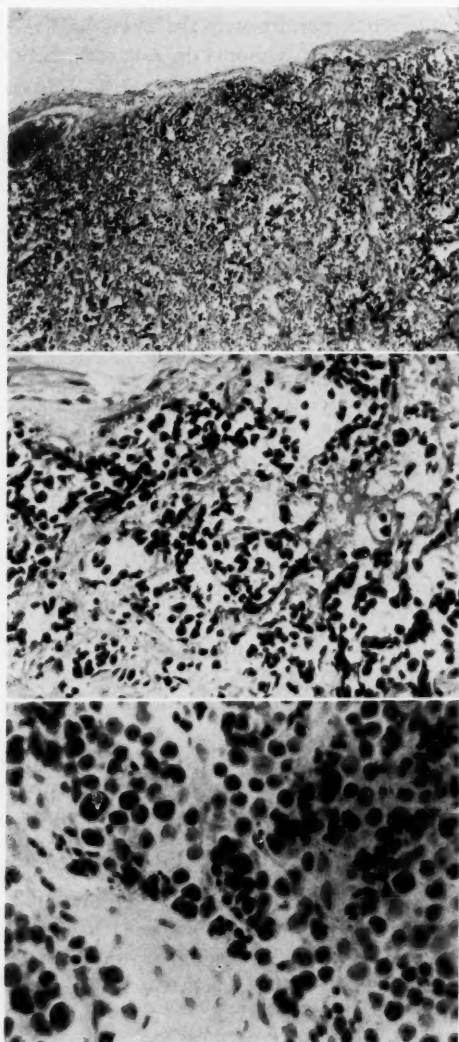


Fig. 1.—Low power photomicrograph of section of tracheal adenoma showing, from above downwards, stratified epithelium, loose connective tissue capsule, and regular structure of the tumor proper.

Fig. 2.—High power photomicrograph of section of tracheal adenoma showing masses of epithelial cells with a tendency to form acini.

Fig. 3.—High power photomicrograph now showing malignant changes, characterized by variation in size of the cells and staining properties.

into the anterior wall of the esophagus about the level of the third tracheal ring.

Microscopy now revealed malignant changes, characterized by variation in size of the cells and staining properties (Fig. 3).

Following the removal of the skin sutures on the seventh day, the patient had a severe convulsion, accompanied by vomiting, following which the wound broke down.

The convulsive seizure was controlled by 10 cc of a solution of calcium gluconate administered intravenously. Subsequently the patient was given through the duodenal tube 4 cc of calcium chloride solution and 100,000 units of vitamin D daily. Thyroid deficiency demonstrated itself about six weeks following operation, and was controlled by thyroid extract, gr. 1, daily.

A small recurrence in the skin was removed in January, 1949. The patient is at present well. Closure of the pharyngeal fistula is to be undertaken when it is felt certain that there is no further recurrence. There is no evidence of enlarged cervical glands.

SUMMARY

1. Tracheal adenomata are rare. Three cases have been recorded in the literature, a fourth case is here reported.
2. They are benign tumors, but like mixed salivary tumors which they closely resemble, should be considered locally malignant, due to their ability to infiltrate in a limited way. Tracheal adenomata, like bronchial adenomata, show a uniformity of structure and staining properties, a tendency to glandular formation with no sign of unruly growth. Metastatic spread has never been reported and extension of the tumor is never a cause of death.
3. The only symptom of adenoma of the trachea is dyspnea, which occurs late in the course of the tumor.
4. Evidence is produced that tracheal adenoma should be treated by external surgical removal.

702 MEDICAL ARTS BLDG.

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CVII

RESECTION AND ANASTOMOSIS OF THE TRACHEA:
AN EXPERIMENTAL STUDY

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O. THERON CLAGETT, M.D. (By Invitation)

AND

HERMAN J. MOERSCH, M.D.

ROCHESTER, MINN.

The purpose of this report is to describe the results one and one-half to two and one-third years after resection of a portion of the trachea in a series of 7 dogs. In a previous report we related our early studies on resection of the trachea. In that report¹ early data on the present series of dogs were included. At the time of the first report this series of dogs had been observed for two and one-half to thirteen months.

Resection of a portion of the trachea in the dog was found to be a relatively simple procedure. The upper two-thirds of the trachea is easily accessible through a midline cervical incision when the dog is in the supine position and the neck and head are extended. The lower third may be exposed without difficulty through a high right thoracic incision. Our technique of anastomosis was designed to obviate the difficulties which we anticipated would prevent successful restoration of continuity of the trachea. The technique permits an anastomosis to be made simply and quickly which does not leak air and does not cause narrowing of the tracheal lumen. The anastomosis is made over a polythene (polyethylene) tube which has approximately the same inside and outside diameter as the trachea, and has three narrow, external ridges, one in the middle and one about 2 mm from each end. A method of making such tubes by fusing thin layers of polythene film together over a tubular mold has been described in a separate report.² We have found that the length of a tube should be two and one-half times its diameter.

After the segment of trachea to be removed has been freed from surrounding tissue, incisions are made between the rings of

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

cartilage at each end of the segment. These incisions are carried through only half the circumference. The segment is then split longitudinally, and traction sutures of heavy silk are placed at each end of the trachea. The polythene tube is inserted through the split segment and, while an assistant uses appropriate traction on the sutures, the two ends of trachea are approximated over the tube. After the traction sutures are tied together additional interrupted silk sutures are placed and removal of the segment is leisurely completed. Several sutures transfix the middle ridge of the tube and thus prevent it from moving or rotating. Leakage of air is prevented by the ridges at the ends of the tube which fit between rings of cartilage and stretch the membrane so that it fits snugly about the tube. Retraction of the ends of trachea, which would make this operation difficult and hazardous, is prevented by the fact that the trachea is not completely divided until the final end-to-end sutures are placed.

Seven in our series of dogs on which resection of a portion of the trachea had been performed were alive at the time of our first report, fifteen months ago. All of these dogs are still living and have remained healthy. The middle part of the trachea had been resected through cervical incisions in 2 animals. A segment consisting of four cartilaginous rings had been removed from one (dog 1*) of these 2 animals twenty-eight months ago, and a segment consisting of five rings had been removed eighteen months ago from the other (dog 2*). Four rings of cartilage had been removed from the lower part of the trachea through thoracotomy incisions in the other 5 animals (dogs 3 to 7*). This operation was performed twenty-seven months ago on 1 (dog 3) and eighteen months ago on 4 dogs (dogs 4-7). None of the 7 animals have cough or signs of respiratory embarrassment. Breathing and breath sounds are normal in all dogs except dog 4. When this dog is excited or is exercised, a slight degree of stridor is present.

Bronchoscopic examinations have been performed by one of us (H. J. M.) on these animals every few months after pentobarbital sodium anesthesia. On the whole there have been few pathologic changes. The polythene tubes are present and in good condition in all animals except dog 6. The tube of this animal which had been noted to fit loosely at previous examinations but was still in place at the examination made twelve months after resection was absent

*For the reader who wishes to compare data published in a previous paper¹ with data in this paper the following list of numbers is given. Dog 1 in this paper was listed as dog 7 in the previous paper¹; dog 2 as dog 8, dog 3 as dog 9, dog 4 as dog 10, dog 6 as dog 12, and dog 7 as dog 13.

on bronchoscopic examination fourteen months after resection. The tube of dog 4 which had the slight stridor during exertion has been noted to fit loosely at bronchoscopic examinations during the past four months.

The tracheas of 4 dogs (dogs 1, 2, 5 and 7) appeared normal above and below the tubes at the time of the last bronchoscopic examination. The appearance of the trachea at the distal end of the tube of dog 3 suggests that the ring of cartilage adjacent to the tube is absent. The trachea at the distal end of the tube appears to be partially collapsed for a very short distance. Although there was a slight space between the tube and trachea of dog 4, the dog with the stridor on exertion, little inflammatory reaction could be discerned on the tracheal mucosa at the upper end of the tube. The only abnormal finding in the dog (dog 6) which apparently had coughed up the tube some time between twelve and fourteen months after resection was a slight irregularity of the trachea at the site of anastomosis. The lumen was not narrow at this point.

COMMENT

Longer observation of our small series of 7 dogs after resection of a portion of the trachea and anastomosis over a special polythene tube has made us conclude that the operation may have some clinical application. At present it appears that a primary tumor which is localized to a few tracheal segments and is above the bifurcation of the trachea may be treated surgically by this method. Recent clinical experience, however, makes us appreciate that tumors are most likely to involve the bifurcation and has led us to seek a method of resection of such lesions but, so far, our efforts have been without success.

We have not, as we first expected, found that the implanted tubes obstructed outflow of bronchial secretions. It is true that, at some bronchoscopic examinations, small bits of mucus have been found in the region of the tube but we have never seen signs of retention of appreciable amounts of mucus distal to the tube. Absence of cough supports our belief that outflow of mucus is not significantly impeded, despite the fact that there is an interruption of continuity of the ciliated epithelium of the trachea. Presumably, the back-and-forth movement of air during respiration maintains a balance between the amounts of mucus at each end of the tube. Mucus does not coat the wall of the tube itself because polythene, like its much less polymerized form, ordinary paraffin, is not wetted by aqueous solutions and will not cohere to other substances.

It is significant, also, that the implanted tubes do not appear to deteriorate and do not seem to act as irritants. That this would

be true might be expected because at room and body temperatures, polythene is not affected by solvents, chemicals or physical agents.

The results in 4 of the 7 dogs (dogs 1, 2, 5 and 7) of the series are excellent. We believe that the poor result in dog 3 was caused by the fact that the tube was slightly too large in diameter, that it stretched the distal, adjacent ring and caused absorption of its cartilage. The diameter of the trachea at this narrow point of partial collapse, however, is still adequate and does not appear to be decreasing. It would seem, also, that the observations that the tube in dog 4 fits slightly loosely and that the tube in dog 6 has been coughed out indicate that these tubes were slightly too small in diameter and probably too short as well. Our conclusion, that a tube should be of the same diameter as the trachea and that too large a tube is worse than too small a tube, is supported by observations made earlier in our work.

In our previous report we found that tracheal collapse and death from asphyxia was likely to result when tubes which had been too large were removed. We found also that tubes which were too small in diameter and short for the main bronchus in which they were implanted in 2 dogs were coughed out. It is interesting that these dogs are still well and that stricture has not occurred at the site of the tube and that the same favorable result has occurred in dog 6, which coughed up its tracheal tube. Our first report described the early results of surgical removal of a properly fitting tube from 1 dog. This dog remained well for almost a year and then died of perforation of the stomach caused by a sharp splinter of bone. Necropsy showed a well-healed anastomosis with normal lumen of the trachea, although three rings of cartilage in the region of the anastomosis had been partially absorbed and were incomplete.

Our studies prompt us to draw certain conclusions concerning the principles of anastomosis which are prerequisite for successful resection of the trachea. Above all, the tube must not be larger in diameter than the trachea. If a tube which is too large is allowed to remain in place, it is likely to cause absorption of adjacent rings of cartilage and it cannot be removed unless it is replaced by a longer tube of the proper diameter. A tube which is less than the diameter of the trachea will fit too loosely and is likely to become dislodged. On the other hand, tubes of small diameter apparently may be removed safely. Whether tubes which are of the right diameter may be removed or not depends on whether or not the ends of the trachea were approximated over the tube at the time of anastomosis. If the ends were brought together, enough of the rings of cartilage may remain to prevent collapse when the tube is removed. If the

ends of trachea cannot be approximated and the gap has to be bridged by fibrous tissue which forms over the tube, collapse of this fibrous portion of the trachea will occur when the tube is removed. Tubes which are shorter than two and one-half times their diameter not only make the anastomosis technically difficult but, according to our experience, tend to irritate the adjacent ends of trachea.

SUMMARY

Two dogs have been observed for more than two years and 5 dogs for a year and one-half after resection of a portion of the trachea and anastomosis over special polythene tubes. The dogs are well and bronchoscopic examinations reveal few signs that the tubes which are still in situ in 6 dogs are injurious. The only abnormal findings concern 2 dogs in one of which the tube was too large and in the other too small in diameter; in the former there is a short area of partial collapse of the trachea distal to the tube, and in the latter the tube fits loosely. One dog lost its tube about a year after operation, presumably because it was too small in diameter and became loose. This dog is well and the trachea at the site of anastomosis is marked only by slight irregularity.

MAYO CLINIC.

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CVIII

STRICTURE OF THE ESOPHAGUS FOLLOWING PREGNANCY

A CASE REPORT

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REPORT OF A CASE

M. S., a white female aged 29, was admitted for esophagologic study on May 19, 1939. Her chief complaint was dysphagia for solids since the delivery of her first child at another hospital, December 13, 1938.

History. She had measles, chicken pox, pneumonia and paratyphoid fever during the first six years of life. Since then she has been perfectly well other than occasional colds and influenza. She was married at the age of 25, and has had but one pregnancy.

Course of Pregnancy. There was slight vomiting once or twice during the first three months of pregnancy. She was in excellent health during the remainder of her gestation. She ate and slept well, gained 25 lb. above her normal weight of 105, and her labor was induced approximately two weeks before the term. The labor lasted 48 hours, 22 hours of which the patient was on the operating table. The baby was delivered by means of forceps. So-called twilight sleep was used for a period of 18 hours and toward the end of the second stage she was given a quantity of some form of vapor anesthesia which the patient thought to be chloroform. The exact amount of the drug used could not be determined; but some of it was accidentally spilled into her mouth and swallowed. The development of the stricture was attributed to that occasion by the patient. There were large, multiple perineal tears, requiring several stitches for repair. She was in a state of shock and part of the time delirious. The day following delivery she suffered from severe headaches and pain in the roof of her mouth. The second night following delivery she began to vomit violently at close intervals. Vomiting

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Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

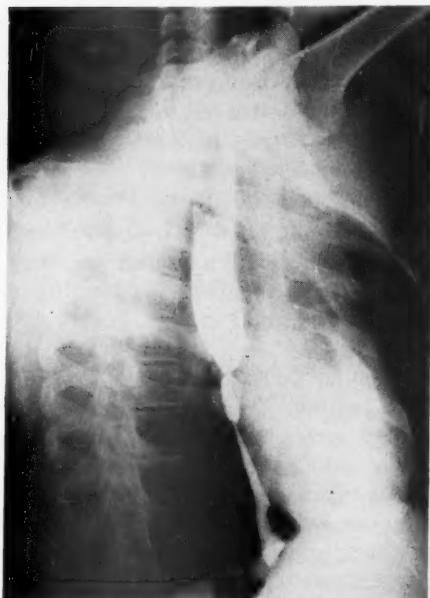


Fig. 1.—Roentgenogram of the esophagus with barium, showing multiple strictures in the lower half. The proximal portion is slightly dilated.

ing continued for several hours. There was an intense substernal pain for which she received several doses of opiates. On the third day she developed marked jaundice, lasting for eight weeks. She was dismissed from the hospital on the ninth puerperum day. During the period of convalescence in the hospital, she could not keep anything on her stomach but liquids. She was under the care of a special nurse for six weeks at home. Convalescence was slow. Soon after reaching home, she found that she was not able to swallow solids and was kept on liquids and soft foods only. She had been living on soft foods until she came to my service.

X-ray Examination. Films revealed multiple strictures of the esophagus; the first at the level of the seventh and eighth dorsal vertebrae. There was no complete obstruction to the passage of barium meal, but the proximal portion of the esophagus was slightly dilated. Below this area of stricture there were several others. There was no evidence of constriction in the upper portion of the esophagus (Fig. 1).

Esophagoscopic Examination. On the first visit the upper third of the esophagus presented normal endoscopic appearance. At a point 27 cm from the upper incisor teeth there was a concentric stricture which readily yielded to gentle dilatation up to bougie No. 28. Beyond this strictured area, slightly off the center, there was another area of stricture which the examining instrument failed to reach on account of the first stricture. The patient reacted well to the treatment and was sent home the following day.

Subsequent Dilatations. For a period of six weeks she had weekly dilatations. This was lengthened to every three or five weeks and later to every six months. She is maintaining her normal weight and is free from discomfort.

ETIOLOGY OF STRICTURE

According to Jackson,¹ "there is always ulceration and erosion, and later secondary pyogenic infection. This is often followed by healing with cicatricial contraction and organic stenosis." As to the primary etiology Jackson mentions trauma, cauterants, numerous infectious diseases and neuromuscular disorders. He states that "digestion of the esophagus and perforation may result from the stagnation of regurgitated gastric juice therein." This condition sometimes occurs spontaneously in profound toxic and debilitated states.

The literature on stricture of the esophagus following vomiting in pregnancy is extremely meager. Vinson²⁻⁴ is the only writer on the subject. In 1921, he reported six cases that were observed in the Mayo Clinic since 1911. In 1923, he recorded three additional cases. By 1927 he had seen a total of 13 cases. He noted that the vomiting of blood or dark-colored material was a prominent symptom in five of his nine cases, and in another a peri-esophageal abscess had ruptured into the esophagus. Six had substernal or epigastric pain. All of the lesions were located in the lower half of the esophagus. He, too, thought the strictures represented the healed stage of a digestive process which occurred in the esophagus during life. Butt and Vinson⁵ believe that vomiting alone can produce esophageal strictures. Elaborating on the mechanism of pathogenesis they state that stretching of the esophagus in vomiting with a possible small break in the mucous membrane and increased peristalsis lend themselves to the development of esophagitis.

Mosher⁶ has shown that "the esophagus can be infected from within and from without, and is often infected in both acute and chronic diseases. In the esophagus, fibrosis follows infection, as it does in other organs of the body. As the esophagus is so frequently

infected, there is abundant cause for stricture or fibrosis to occur in any part."

On the process of development of ulceration of the esophagus, stomach, biliary tract and the intestine following operation, Penner and Bernheim^{7, 8} state that there is a series of vascular changes in response to the presence of shock. First, there is vascular contraction. This is accompanied by anoxemia of tissue, followed by a drop in the gradient of intracapillary pressure, leading to an increase in capillary permeability. There occurs a transudation of plasma protein into the tissue spaces; this in turn is followed by punctate hemorrhages into the tissue and final necrosis and formation of pseudomembrane.

Bloch⁹ reports on 26 cases of acute, ulcerative esophagitis found at necropsy. Fourteen had been operated on; ten for disorders of the gastro-intestinal tract. Bloch found 11 patients who were operated on suffered from what might well be considered shock. Necropsy in other patients dying of shock showed no changes in their esophagus. Other etiologic factors undoubtedly play a part. Embolism and thrombosis are favored by the presence of large venous channels in the lower portion of the esophagus. He concluded that no definite factor is known. There are several contributory ones. Among them he mentions vomiting, trauma from the Levine tube, shock, severe general and focal infections and involvement of the central nervous system.

ANIMAL EXPERIMENTATION

Seven healthy rabbits weighing $4\frac{1}{2}$ - $4\frac{3}{4}$ lb. (2025-2137 gm) were selected. Chemically pure chloroform, 0.25 cc, 0.50 cc, 1.0 cc, and 2.0 cc, was placed at the base of the tongue by means of a silver cannula. The animals tolerated this procedure. Upon swallowing the drug each shrieked for a moment. The one receiving 0.25 cc of the drug was sacrificed at the end of 96 hours. The three having received 0.50 cc or more all died within three days, having vomited dark-colored gastric contents as a terminal episode.

Inhalation anesthesia was given in one. The rabbits are extremely sensitive to vapor of chloroform and it was found to be practically impossible to keep the animal alive for any length of time for my purposes. To study the systemic effects of the drug, 0.5 cc and 1.0 cc of chloroform were introduced intramuscularly. The animal which received 0.5 cc died in 60 hours. The other was sacrificed in 48 hours.

At necropsy the esophagus measured 13-15 cm in length and held an average of 1.2 cc of liquid without stretching. Upon section-

ing longitudinally, the esophagus of the animals which received intra-oral medication, contained various amounts of a thin layer of fibrinous exudate. The most pronounced change was noted in the appearance of the liver. It had a reddish tinge, easy to tear and mushy in cutting. Microscopic examinations of the esophagus showed cellular debris and leukocytes within the lumen. There was desquamation of the more superficial layers of the stratified squamous epithelium of the esophagus with pyknosis and evidence of death of the stratified squamous epithelial cells extending for a considerable depth. The stratified squamous epithelium in a few areas showed necrosis and ulceration down to and including the basal layer. The more peripherally located fibrous connective tissue structures beneath the epithelium were densely infiltrated in some areas with leukocytes and there was evidence of necrosis of the fibrous tissue stroma. The muscular coats of the esophagus were free from inflammatory changes (Fig. 2).

Sections from the specimens of the liver showed central necrosis of the liver lobules with only a thin rim of viable cells about the periphery of each liver lobule. In the greater portion of the liver parenchyma the cells were undergoing karyorrhexis. The cytoplasm of many of the cells was fragmenting. The parenchyma of the liver about the periportal areas, although still maintaining the normal architecture of the liver, showed evidence of toxic changes with pyknosis of the nuclei and some fine reticulation of the cytoplasm. There was no apparent increase in the round cell infiltration of the fibrous tissue about the periportal structures (Fig. 3).

A section from the trachea showed complete coagulation necrosis of the mucosal lining with dense infiltrations of polymorphonuclear leukocytes in the submucosa and extending to the cartilage rings (Fig. 4).

A section of the lung showed many of the small bronchioles filled with leukocytes and having necrosis of the bronchial mucosa. The lung parenchyma adjacent to these bronchioles was infiltrated with leukocytes and many of the alveolar spaces were filled with edema fluid and red blood cells. The bronchopneumonia in many areas was confluent (Fig. 5).

The two animals which received intramuscular medication showed the following changes: The liver had undergone acute yellow atrophy, similar to that seen in animals treated by the intra-oral route. The heart of one of the animals showed focal areas of round cell infiltration of the myocardium. The other was normal. The spleen of both animals showed marked passive congestion. The

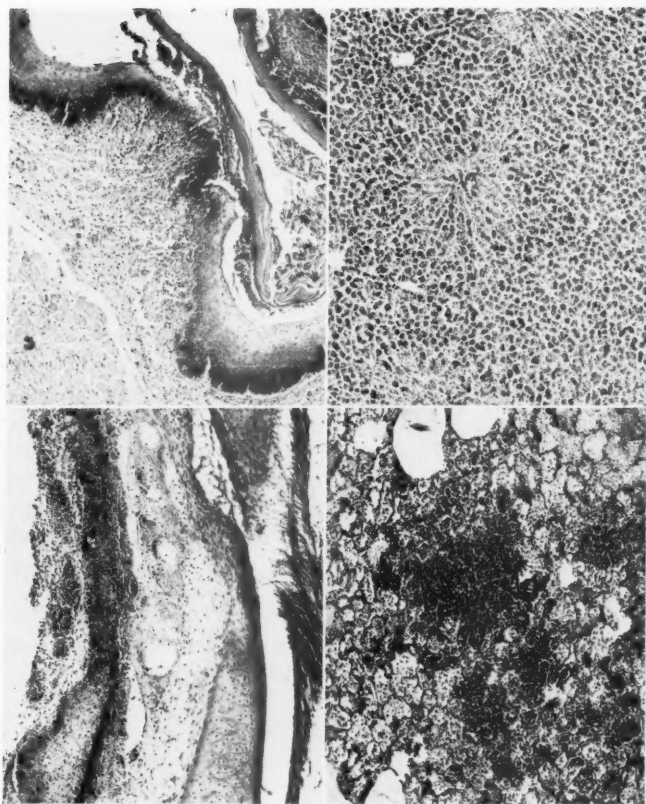


Fig. 2.—Photomicrograph of esophagus of rabbit which received intra-orally 2 cc of chloroform and swallowed. The superficial layers of stratified squamous cells are desquamated. In a few areas the squamous cells have undergone necrosis and ulceration down to the basal layers. The submucosa is densely infiltrated with polymorphonuclear leukocytes. The muscular coats are not involved.

Fig. 3.—Photomicrograph of the rabbit's liver showing central necrosis. This animal received intra-orally 2 cc of chloroform and swallowed. Note fragmentation of cells and karyorrhexis of the nuclei.

Fig. 4.—Section of the trachea of rabbit which received intra-orally 1 cc of chloroform, some of which was aspirated. Note the massive coagulation necrosis of the ciliated columnar epithelial cells and dense infiltration of polymorphonuclear leukocytes.

Fig. 5.—Photomicrograph of section of the lung of the same animal as in Fig. 4. Note the diffuse pneumonitis.

trachea and the lung showed a slight degree of congestion. The esophagus was normal in appearance throughout the mucosa, tunica propria and muscular coats.

COMMENT

The patient attributes her esophageal stricture to the ingested anesthetic agent as the primary cause of her disorder. Neither the nature nor the amount of anesthetic agent used is known. The patient thought it to be chloroform. During its administration, a portion of the drug is alleged to be spilled on the face and swallowed. The roentgenogram is suggestive of stricture from corrosive poisoning. Bastedo¹⁰ states that chloroform is a general protoplasmic poison of considerable destructive power. If concentrated, it will cause the death of tissue with which it comes in contact. Even when dilute, as in the blood, it can readily produce degenerative changes in various organs of the body. In clinical practice, however, chloroform is seldom used so as to saturate the anesthetic mask, certainly not in amounts to let it drip into the patient's mouth to cause coagulation necrosis of the esophagus. This is the most difficult part in accepting the theory of ingestion.

Inhalation anesthesia lasted four hours toward the end of the second stage of her labor. In the presence of overwhelming toxemia the liver cells are the first to suffer and show the evidence of injury. The fact that this patient continued to suffer from jaundice for a period of eight weeks indicated that there was a definite liver damage. Bastedo states that doses of chloroform incapable of causing recognizable injury may decrease secretion of bile salts. In hepatic disorder, conversion of vitamin K to prothrombin is greatly impaired. Lowered prothrombin predisposes to hemorrhage. Is it possible that hemorrhage from the esophagus was a factor in this patient's esophageal stricture?

She also continued to vomit violently for several hours after parturition. Alvarez and Moersch,¹¹ of the Mayo Clinic, state that 20 years ago they had observed a number of cases of stricture of the esophagus following vomiting in pregnancy; but in recent years they had seen none. Dr. Moersch attributed the fewer incidents of strictures to the better care given to pregnant women by obstetricians who control vomiting earlier. Every one who vomits does not develop esophageal strictures. However, that vomiting at times does cause cicatricial stenosis has been amply demonstrated. Just what was the primary factor in development of strictures in this patient is not easy to determine. There may be several contributory factors.

Treatment is no different from other forms of benign strictures of the esophagus. A periodic, systemic dilatation by bouginage gives the best result in restoration to a nearly normal lumen.

SUMMARY

A case of postpartum, esophageal stricture in a 29-year-old, white woman is recorded. Clinical signs and symptoms are suggestive of corrosive reaction to accidentally ingested chloroform rather than inhalation of the vapor. Long continued, violent vomiting following delivery cannot be ruled out as a factor in development of the strictures.

436 SOUTH BOYLES.

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CIX

AN UNUSUAL ACCIDENT WITH AN AEROSTATIC DILATOR

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REPORT OF A CASE

This patient, a male aged 37, had suffered intermittently from the symptoms of cardiospasm for a period of 15 years. X-ray examination in 1936 had shown an extremely dilated esophagus. He had satisfactory symptomatic relief following aerostatic dilatation and his last treatment was in January, 1944. He returned in July, 1947, with a chief complaint of chills and fever of three days' duration. His temperature at that time was 103° F. He said that he swallowed without difficulty except when he was excited and then he would regurgitate indicating that overaction of the sympathetic nervous system does tighten the cardiac sphincter.

Fluoroscopic examination revealed a greatly dilated esophagus measuring 8 cm in diameter from the level of the clavicles down. It contained a large quantity of fluid and food particles. The distal 10 cm was redundant and ended sharply in a cone-like point. Barium entered the stomach in a thin trickle. He was given penicillin, 50,000 units intramuscularly every three hours, day and night, and a No. 54 French scale mercury-filled bougie was passed into the stomach without difficulty. His temperature was normal within 48 hours.

Esophagoscopy showed considerable retention of food debris and the mucosa was covered with pasty gray exudate. There was no evidence of infection elsewhere in the body so his fever was attributed to acute esophagitis. Five days after his admission he was symptom free and was swallowing without difficulty. An aerostatic dilator was introduced and fluoroscopic examination showed that the dilating bag was in the stomach. It was withdrawn 3 in. and was inflated until the pressure on the dial read 1½ lb. This caused moderate pain so the bag was deflated. Even after deflation it was found that the bag could not be withdrawn, using such traction as

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

was deemed safe. The patient was given 100 mg of demerol subcutaneously and a half hour later another attempt was made to withdraw the dilator. Fairly strong traction would not withdraw the bag, so the patient was again checked at the fluoroscope by Dr. Hinkel. The dilating bag was in the stomach, but the barium stripes indicated that the bag was not distended. Both the patient and the doctor were perspiring freely. Very firm, continued, steady traction finally withdrew the dilating bag when it was found that the outer rubber covering was distended with air to a diameter of almost 2 in. The rubber bag inside the cloth bag carrying the barium stripes was collapsed. Obviously the inner rubber bag had developed a perforation which acted as a one-way check valve permitting air to enter, but not escape from the outer rubber covering. The patient had no ill effects and has had only slight occasional dysphagia since that time. He gained 24 lb. in weight and has required no treatment during the past 12 months.

GEISINGER MEMORIAL HOSPITAL.

CX

A METHOD OF CONCEALING STRING IN CASES
REQUIRING RETROGRADE DILATATIONS
OF THE ESOPHAGUS

MURDOCK EQUEN, M.D.

ROBERT BROWN, M.D. (By Invitation)

AND

GEORGE ROACH, M.D. (By Invitation)

ATLANTA, GA.

The seriousness of esophageal stricture has been recognized by the medical profession more than a hundred years. Blind passage of bougies from above was too often fatal. The guidance of the bougie on a swallowed string was better, but it was not always possible for the patient to swallow the string. In 1893, Abbe¹ stated, "It remained for Albert to do the first case of dilatation of the esophageal stricture through the stomach and save his patient." Abbe in that paper reported a case in which a string was introduced through the stomach and up through the mouth to permit retrograde dilatation. Plummer and Mayo in 1894² and, more recently, Tucker,³ have improved this technique.

The value of this method cannot be questioned, but it has certain disadvantages. The string must remain in place, not for days or weeks, but often for months, if not years. It is embarrassing to the patient to have a string across his face. When he has to meet the public it is a real economic handicap. Moreover, when a patient swallows spontaneously the string is carried further down and rendered taut, thus cutting the edge of the nostril. A third drawback is that the string crosses the soft palate causing irritation and gagging, and even nausea.

To obviate these difficulties the string is attached to a removable bridge in the lower jaw.

From the Ponce de Leon Ear, Nose and Throat Infirmary.

Read before the meeting of the American Broncho-Esophagological Association, Chicago, Illinois, April 18-19, 1949.

REPORTS OF CASES

CASE 1.—In the summer of 1930, a child of 4 swallowed a textile bobbin. Two years later she was suffering from starvation and dehydration and so gastrostomy was performed. When she was brought to consult one of us (M. E.) on January 10, 1933, the bobbin was firmly fixed midway in the esophagus, and 1 cm of dense scar tissue completely occluded the lumen above the bobbin. With a specially devised knife manipulated through an esophagoscope, under the guidance of a biplane fluoroscope, it was possible to cut through this scar tissue and grasp the bobbin with forceps. The bobbin was then pushed down into the stomach and removed through the gastrostomy. This case was originally reported in the *Journal of the American Medical Association* in 1934.⁴

Although the child was told to return for periodic dilatations, she did not show up again until November, 1948. For a number of years after the removal of the bobbin, she had been able to swallow but she had continued to take food also through the gastrostomy tube. Despite these difficulties she had secured a college degree. When romance appeared in her life she had the tube removed and the gastrostomy closed; after that she had to live on a practically liquid diet. She was, however, still supporting herself teaching in high school.

On her return in November, 1948, she was a very thin young lady (5 feet tall, weighing 80 lb). X-ray examination revealed marked dilatation of the lower cervical and upper thoracic parts of the esophagus. There were multiple irregular zones of narrowing involving the lower two-thirds of the thoracic esophagus. After the gastrostomy had been reopened, an esophagoscope was passed down as far as possible. Then a tiny steel cone attached to a thin semiflexible wire was passed through the very small lumen of the stricture into the stomach.

A magnet was dropped into the stomach through the abdominal opening to retrieve the cone. After tying a string to it, the cone was pulled back up the esophagus through the mouth leaving the string in the esophagus. Retrograde dilatations were then carried out in the usual manner.

The string from the nose across the face was disfiguring and attracted so much attention from her young students that the situation became intolerable.

The problem was solved by her dentist, Dr. W. B. Webb, of Gadsden, Alabama, who devised a removable bridge across the

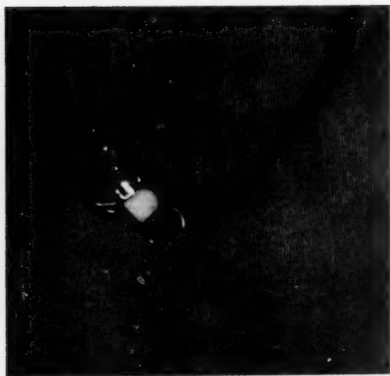


Fig. 1.—The removable bridge with string attached.

site of a missing tooth in the lower jaw, and to this bridge the string was tied (Fig. 1).

By April 8, 1949, the girl had gained 8 lb. after monthly dilatations, which must of course be continued. Immediately after each dilatation she easily swallows normal food, but she has some difficulty swallowing before the month is over.

CASE 2.—A widow, aged 36, in a fit of depression swallowed lye. She was acutely ill for two weeks and then could only swallow liquids and semisolids. X-ray examination revealed the diameter of the thoracic esophagus to be 4 mm. A gastrostomy was performed and a string was introduced as in Case 1. This lady, too, had to support herself and therefore objected to the string across her face. She objected, too, to a removable bridge. Dr. Charles Smith devised an acrylic to fit below and behind her lower teeth (Fig. 2); near one end of this appliance he fixed a ring to which the string could be tied.

CASE 3.—A 20-month-old infant was brought into the Infirmary with a history of swallowing powdered lye three weeks previously. She was gravely dehydrated and crying for water which she could not swallow. After subcutaneous fluids were administered, a gastrostomy was performed, and a string was threaded through the esophagus as in the first two cases.

After a few dilatations the child refused to open her mouth, making it necessary to anesthetize her to make a cast of her mouth. From this cast, Dr. Charles Smith prepared a cap of alloy to which

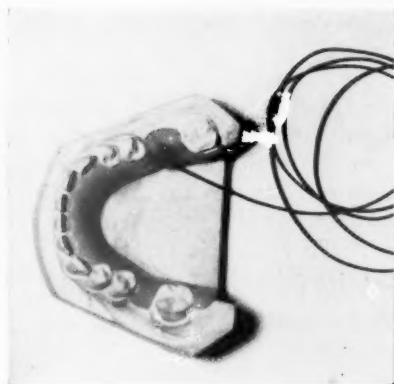


Fig. 2.—The removable acrylic apparatus with the string attached.

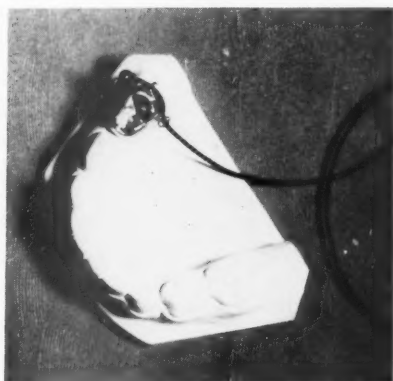


Fig. 3.—Cast of the child's lower teeth with the dental cap.

he attached a ring (Fig. 3), the child was anesthetized again and this cap was fixed to a deciduous lower molar. The string was tied to the ring. The child was so pleased after she had seen her shining dental cap with a mirror, she was quite delighted to open her mouth to exhibit her "new tooth," until we tried to photograph her showing the cap in place.

SUMMARY

In cases of stricture of the esophagus that are severe enough to require a string in the esophagus for a long period of time, to have the string brought out through the nose is disfiguring and embarrassing to the patient. It tends to cut the nostril and to interfere with swallowing. To meet this problem it is suggested that the upper end of the string be tied to a dental gadget.

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Abstracts of Current Articles

EAR

Tympanosympathetic Anesthesia for Tinnitus Aurium and Secondary Otalgia.

Trowbridge, Barnard C.: Arch. Otolaryng. 50:200-215 (Aug.) 1949.

By interrupting the nerve impulses carried along the pathway of the tympanic plexus, the author has succeeded in completely, and evidently permanently, abolishing or partially alleviating peripheral intrinsic tinnitus and referred otalgia in a majority of cases treated. He has developed a technique of injecting the tympanum with a 5% solution of ethylmorphine hydrochloride at specified intervals, which permits patients to remain ambulatory, causes them little discomfort, has resulted in no significant side-reactions and no deleterious after-effects.

The basis for his work is laid in a detailed study of the anatomy and histology of the ear and clinical and experimental observations which are presented in a lucid manner. The technique and materials used in the injection are described. Criteria for the selection of patients are given with the admonition that to attain good results, cases must be carefully selected. A series of 20 patients is listed in which the majority obtained good results, 9 experienced partial relief and only 2 reported no improvement. A previous series of 20 is mentioned, in which hearing acuity was studied before and after the injection therapy; improvement in hearing resulted in 18 of these patients; the number of those with tinnitus receiving complete or partial relief was smaller because the technique was improved at the time of the second series.

HILDING.

Otosclerosis: Theory of Its Origin and Development.

Lempert, Julius, and Wolff, Dorothy: Arch. Otolaryng. 50:115-155 (Aug.) 1949.

The authors, in 1945, reported a series of 115 cases in which they examined the ossicles to determine how frequently otosclerosis involves the incus and the malleus in the presence of an otosclerotic lesion within the otic capsule. Completely normal ossicles were found in only five instances; the ossicles, which presented no typical

circumscribed foci of otosclerosis—such as found in the otic capsule—did show numerous pathologic changes in the joints, marrow spaces and bone, particularly in the blood vessels of the ossicles.

A second series of ossicles removed from 100 patients having fenestration of the labyrinth for clinical otosclerosis is the subject of their present report. The study includes the incus, head and neck of the malleus and occasionally the head and crura of the stapes. Again, only four normal ossicles were found and the previous findings—ossicles showing no typical circumscribed focus of otosclerosis comparable to the demarcated pathologic area occurring in the otic capsule in otosclerosis, but pathologic changes occurring in the joints, bony tissue and marrow spaces of the ossicles, particularly the blood vessels—were duplicated.

They felt the lesions occurring in the ossicles were a part of the otosclerotic process observed in the otic capsule and postulate the reason the lesions in the ossicles are not circumscribed by healthy bone lies in their more meager blood supply. Because they found the outstanding histologic feature of the two series of ossicles studied to be the constantly occurring blood vessel pathology, similar to that seen in the blood vessels of otosclerotic foci within the otic capsule, they carefully observed the pathologic changes in the blood vessels and correlated these observations with the pathologic changes in the bony structure of the ossicles. This enabled them to entertain the theory that vascular changes most likely preceded, and were responsible for, the pathologic changes in the bony structure known as otosclerosis.

Study of the ossicles in the 100 patients of the second series showed the following progressive stages in their probable chronologic order:

Changes in the Contents of the Blood Vessels: Clear globules, accumulating fragmented red blood cells, sludge and accumulating polymorphonuclear leukocytes. *Changes in the Vessel Walls:* Constriction of the venules and arterioles, tortuosity due to hypertrophy of endothelial cells or varicosities, periarteritis and endarteritis. *Pathologic Changes of Bone:* An excess of blue mantles, hypervascularity, decalcification (after decalcification patients react in different ways, according to individual constitutional make-up), osteofibrosis, osteoporosis, malformations and exostoses, ankylosis (incudostapedial and incudomalleolar points) and ischemia with lacunas devoid of bone cells.

One ossicle may present any one or a combination of several types of the pathologic processes involving bone, each patient react-

ing differently to the presence of the disease. The lesions themselves are minute in size but their strategic location makes them significant. Senescence was ruled out in this series as an etiologic factor because the largest group fell between the ages of 20 and 50. The authors believe the initial pathologic changes are within the blood stream.

HILDING.

Clinical Examination of Vestibular Disturbances Due to Streptomycin.

Boutiere, Jean: Revue de Laryngologie, Otologie, Rhinologie 70:244-285 (May-June) 1949.

The author reports on his observations on 73 patients at the Salpetriere in Paris, all under treatment for tuberculosis by means of streptomycin, as to the effect of the drug on eighth nerve function, both the cochlear and the vestibular portions. He found that patients treated with streptomycin for a long period (more than one month) usually showed some evidence of vestibular disturbance (in 72% of his cases). Vestibular disturbances were more apt to occur when a larger daily dose of streptomycin was given; 66% when 1 gm per day was given; 84% when 2 gm per day was given. The age of the patient was not a significant factor.

The usual disturbance consisted of an attack of vertigo, more or less intense, with loss of equilibrium, accompanied by nausea, vomiting and visual disturbance. Examination of the labyrinth revealed either hypofunction or loss of response to stimulation (caloric and rotatory tests). This lasted anywhere from a few days to several months. No deafness was found in any of the patients; only two patients complained of vertigo.

HARKINS.

Chorda Tympani Nerve Section and Tympanic Plexectomy. New Technic Used in Cases of Deafness, Tinnitus and Vertigo.

Rosen, Samuel: Arch. Otolaryng. 50:81-90 (July) 1949.

Previously the author reported on a new technique used in surgical fenestration of the labyrinth wherein the chorda tympani was avulsed from its attachment to the facial nerve and was laid over the fenestra nov-ovalis as a pedicle graft, being thus interposed between the membranous labyrinth and the tympanomeatal flap. The purpose was to reduce the incidence of postoperative labyrinthitis by mechanically protecting the membranous labyrinth and peri-

lymphatic space with the chorda tympani. Comparison of the post-operative results in these patients with those obtained by routine fenestration technique showed that the chorda tympani technique resulted in less decibel loss (5-20 db better) than the routine procedure.

The results in eight consecutive patients operated on by the author using this new technique are reported one year postoperatively. All eight were considered to have a successful result (30 db or better) and six of the eight had normal hearing (15 db). Certain patients having very severe tinnitus, vertigo and deafness had experienced prompt relief of symptoms following a one-stage operation combining fenestration, section of the chorda tympani and tympanic plexectomy. A description of the technique is presented and two cases are reported. Adequate preparation on the part of the surgeon necessitates perfection of the technique on the cadaver before attempting it on living subjects.

The author's search for an explanation of the phenomena encountered led him to the formation of an hypothesis based on D. E. Schneider's new theory of hearing. Rosen postulates that the procedure of cutting the chorda tympani and using it as a graft to protect the membranous labyrinth may have, in addition to the mechanical (protective) effect, a physiologic effect by interrupting irritative impulses traveling to the labyrinth via the chorda. In his experience, fenestration alone has failed to produce the speedy return of good hearing, the high degree of recovery of hearing or the dramatic abolition of vertigo experienced by patients subjected to the new operation. He is conducting further research to ascertain the validity of his assumption that these results he has attained may be due to the influence that section of the chorda tympani has on the internal state of the labyrinth.

HILDING.

Effect on the Ear of Vitamin A Feeding after Severe Depletion.

Perlman, H. B.: Arch. Otolaryng. 50:20-35 (July) 1949.

Vitamin A is a factor specifically concerned with growth of the bony skeleton. In vitamin A-depleted animals changes occur in the temporal bone which are described as an apparently excessive periosteal bone formation on its inner surface, involving the internal acoustic meatus. This new bone formation causes narrowing and lengthening of the canal and its contained nerves; despite this narrowing auditory function is not necessarily impaired. The inter-

pretation of these bony changes varies but it is believed that arrest of skull growth results in disproportion between the growing central nervous tissue and the bony skull cage, leading to pressure effects and herniations. (Calcium has been ruled out as a controlling factor in production of the bony overgrowth.) In vitamin A-depleted animals there is a failure to absorb older formed bone to allow for growth of the central nervous system and the laying down of new bone. Overgrowth of the periosteal bone seems to be limited to the otic capsule which some investigators believe due to the fact that the bony labyrinth attains adult size before birth.

Vitamin A depletion in itself is compatible with good auditory function; impairment seems to be secondary to severe compression of the nerve and its vascular supply by new bone in the internal meatus, resulting in widespread degenerative changes. Labyrinthitis is apparently not a primary effect of vitamin A deficiency. The experimentally produced pathologic changes of the temporal bone are rarely encountered in human beings, have not been reported in known vitamin A deficiency states in man, but old pathologic reports describe a condition which resembles this.

To determine the amount of reversal of primary bone changes and secondary neural changes which could be accomplished by feeding vitamin A to depleted animals the authors carried out experiments on rabbits which are discussed in detail and illustrated by many microscopic studies. In the animals depleted and then fed vitamin A, no reversal of new bone formation was observed. The bone became more compact; the large islands of vascular connective tissue were replaced by compact bone. Degenerative changes in the nerve fibers and ganglion cells were not reversed.

HILDING.

Attention to Concealment of Symptoms or Apparent Outward Cures in Penicillin Treatments.

Torii, Eiji, and Morimoto, Masaki: Otolaryngology (Japan) 21:1 (Sept. 1) 1949.

Torii and Morimoto report five cases of otitis media with complicated sequelae, calling attention to the altered picture of this disease subsequent to the advent of the antibiotics (penicillin). Although apparent cure of symptoms in soft tissues may follow the administration of penicillin, the pathological process may continue in the osseous tissues. In this way mastoiditis, apparently cured, may progress leading to meningitis and death. In order to avoid catastrophes from masked effects, they stress the need of thorough

x-ray studies and close following of the progress of the ear disease once it is established, until a complete cure is evidenced by final x-ray examination.

NOSE

Suspension Mechanism of the Upper Lip and the Columella.

Griesman, Bruno L.: *Arch. Otolaryng.* 50:36-44 (July) 1949.

The mechanism of suspension of the upper lip merits study by surgeons operating on the nose because interference with its function is the main danger in surgical treatment of the columella. An anatomical description of the region involved is amplified by a discussion of Langer's lines of normal tension of the skin. Webster is cited as advocating that operative incisions should be made, if possible, in the proper lines of tension of the skin. The complex mechanism of criss-crossed fibers by which the columella and upper lip operate is described anatomically and compared with the extension bracket used to bring forward a telephone or electric light. This action enables the upper lip to continuously change position in speaking, eating and facial expression.

Several operations devised for the correction of deformities of the columella and interrelated procedures on the upper lip have the disadvantage of an external scar resulting from outside incisions. To avoid the external scar and, at the same time, preserve the shifting mechanism of the upper lip, the author has developed an intranasal operation by which the columella, the nasolabial angle and the upper lip can be mobilized and separated by the use of bent scissors directed around the crescent circumference of the septal cartilage toward the nasal spine. The technique and instruments employed are fully detailed.

HILDING.

Role of Compensatory Hypertrophy and Simple Atrophy in Intranasal Surgery.

Evans, James M.: *Arch. Otolaryng.* 50:172-189 (Aug.) 1949.

Nature attempts to retain the bilateral symmetry and aerodynamic balance of the nose by the forces of simple atrophy and compensatory hypertrophy. Evans has developed a corrective surgical technique for different types of cases with nasal symptoms of varying degree, with or without compensatory changes in the turbinate bodies and contiguous structures, utilizing these natural forces

but directing and controlling them according to a carefully planned program. The technique is described. One of the salient features is that the maximum structural rigidity of the septum be preserved. The septum is moved over as nearly intact as possible into the concave side to crowd the hypertrophied structures. After this operation the septum should be in the midline; reduction of the thickened tissues and other structures on the concave side begins and the thinned out tissues on the convex side begin to return to their normal thickness, bringing about normal physiologic functioning. Emphasis is placed on the necessity for adaptation to individual cases and a careful study and complete understanding of the principles before attempting to redesign the compensatory area of the nose.

Nine case reports are detailed and the surgical technique described in each case. These patients presented the usual "sinus" symptoms and included cases of headache, referred pain, allergy and three types of impaired hearing. Minor follow-up adjustments were necessary in some of the cases, but all experienced relief following the corrective surgery. Further treatment was not anticipated. Preventive medicine, the author feels, will benefit by the application of these principles in cases of chronic nasal obstruction.

HILDING.

Incidence of *Staphylococcus Aureus* in the Anterior Nares of Healthy Children.

Cunliffe, A. C.: *Lancet* 2:411-414 (Sept. 3) 1949.

Staphylococcus aureus may be found in the nose and skin of healthy people. About 90% of the nares of healthy infants born in a hospital become infected with *Staphylococcus aureus* during the first two weeks of life.

The nose was sampled by passing a swab moistened with peptone water or nutrient broth through both nostrils. Swabs were taken daily. There was a progressive increase in the carrier rate from 8.6% on the first day to about 100% at the end of the first week, over 50% of the noses being colonized by the third day. There was a rapid fall from 91.5% in the third and fourth weeks to 38.2% in the fourth and fifth months. There was no gross variation in the carrier rate in children born in the hospital and those born at home in the 3 to 12-month age groups.

Swabs taken from mothers within 48 hours of admission to the hospital showed 58% of the mothers to be nasal carriers of *Staphylococcus aureus* and 8% skin carriers.

GROVE.

Treatment of Hay Fever by Injection of the Nasal Mucosa with Alcohol.

Russell, Bedford: Lancet 1:1098-1099 (June 25) 1949.

In preference to desensitizing the patient with antigen or treating the patient with antihistaminic drugs, Russell prefers to desensitize the nasal mucosa with injections of alcohol. If the nasal passages are widely dilated with a spray of neosynephrine and the nasal mucosa is gently palpated with a probe, there are certain areas which, when touched with the probe, react with unbearable tickling, sneezing and lacrimation even before the pollen season arrives. The distribution of these "trigger" areas are, in general, at a lower level than those which occur in the chronic edematous thickenings and polypoid areas of nasal allergy. They are commonly found on the septum about an inch above and behind the mucocutaneous junction. Another common site is the anterior third of the inferior turbinate. A few minutes after spraying the nose with adrenalin these "trigger" zones remain red while the rest of the mucosa is blanched. The "trigger" areas are then injected with 70% alcohol. It is essential to keep the injected alcohol in the mucosa and not introduce it into the erectile tissue beneath. This is done after anesthetizing the mucosa with cocaine. This causes edema and swelling of the sensitive areas and a plastic exudate which can be removed in about four days.

If the patient is first seen after the pollen season has begun it is less easy to inject the mucosa and bleeding may be encountered. At the height of the season Russell avoids the alcohol injection and prefers to paint the sensitive areas with chromic acid. Immediate relief from sneezing and lacrimation is the rule. Contra-indications for this treatment are the presence of inflammation in the teeth or the sinuses and the (rare) existence of characteristic sensitivity over most of the nasal mucosa.

GROVE.

Operative Method for Nasal Basal-Fibroma.

Goto, Toshiro: Otolaryngology (Japan) 21:6 (Sept. 1) 1949.

Surgical removal of nasopharyngeal fibroma is generally regarded as one of the most hazardous operations in the field of otolaryngology. Goto proposes a method by which the growth is exposed through a combined transmaxillary and oral route by separating the soft palate. In this way the base of the growth is made accessible and can be constricted by means of a steel wire. The mass is cut off distal to the constriction with a pair of scissors. The remaining

base eventually sloughs off, along with the steel tie, in about two weeks.

Fibroma in this area arises from the bony structures at the base of the skull, to which the tumor is firmly attached. Because of individual and constitutional susceptibility, recurrences after surgical removal are quite common and cause profuse hemorrhages. The described method, the author states, eliminates troublesome hemorrhages both during and after operation.

LARYNX

Contact Roentgen Therapy in the Treatment of Cancer of the Larynx.

Terracci, J.: Les Annales d'Oto-laryngologie 66:157-161 (Apr.-May) 1949.

In "contact roentgen therapy" for cancer of the larynx, a laryngofissure is performed first, its size depending upon the size of the tumor. The operative wound in the larynx is kept open, for treatment. The laryngeal lumen is kept open by means of a cannula, and the remainder of the laryngeal lumen is packed, around the cannula, with iodoform or vioform, gauze mesh. After eight to ten days the "contact roentgen therapy" is commenced.

The author has, since the end of 1946, treated seven patients by this method, but it is too early to report the final outcome.

The actual technique is presented in the article immediately following this one.

HARKINS.

The Technique of Contact Roentgen Therapy.

Lamarque, P.: Les Annales d'Oto-laryngologie 66:162-167 (Apr.-May) 1949.

This article reported from the same hospital, concerns itself with the actual technique, and is a continuation of the article by Terracci, which is concerned principally with the surgical aspects of exposing the tumor to be irradiated.

Four roentgen treatments are given during an interval of two weeks. A Philips roentgen tube is used, the rays approaching the lesion passing through a small rigid cylinder, called the "localizer," which fits into the laryngofissure wound and is brought directly over the lesion.

HARKINS.

A New Technique for Treatment of Paralysis of the Posterior Crico-Arytenoid Muscle.

Perello, Georges: *Revue de Laryngologie, Otologie, Rhinologie* 70:80-85 (Jan.-Feb.) 1949.

An operative technique is described, in which the thyroid cartilage is exposed through a transverse incision in the neck. The sternohyoid muscle on the side being operated is cut transversely over the thyroid cartilage, and the attachments of the thyrohyoid and sternothyroid muscles are cut, exposing the one ala of the thyroid cartilage. Then a "window" is cut in the exposed ala of the thyroid cartilage, directly over the vocal cord. Here the thyro-arytenoid muscle is exposed and a portion of this muscle is extirpated to a depth of 2 mm. Then the cut end of the upper portion of the sternohyoid muscle is sutured with catgut either to the thyro-arytenoid muscle or to the vocal cord itself. In so doing the cut end of the upper portion of the sternohyoid is turned in through the newly made "window" in the thyroid cartilage. After the operation the patient's neck is kept in flexion for five days to allow union of the sutured muscles, and the patient is fed through a nasal feeding tube.

The author emphasizes that, since the sternothyroid contracts during inspiration, there will be a natural abduction of the vocal cord by the action of this muscle. Also he feels that the naturally occurring descent of the whole larynx during inspiration will cause this portion of the sternohyoid to draw the vocal cord laterally. The relaxation of this muscle during deglutition and the rising up of the larynx during deglutition will allow the vocal cord to move back to the midline; likewise in phonation, these effects, and the elasticity of the vocal cord will leave a good voice.

The author also states that this technique has the advantage that the pharyngeal and laryngeal lumina are not opened during the operation. Furthermore, the amount of abduction obtained can be checked during the operation by an observer, viewing the larynx from above through a laryngoscope.

Unfortunately, no report of any actual cases in which this technique was used are presented.

HARKINS.

BRONCHI**Anatomy of the Bronchial Tree.**

Neil, James H., and Gilmour, Walter: *Arch Otolaryng.* 50:9-19 (July) 1949.

Comparative anatomy is cited in tracing the emergence of the human bronchial tree. The timely question of nomenclature of

some of the segments is discussed and a note appended at the end of the article contains the decisions on terminology reached at the September 1948 meeting of the Otolaryngological Section of the Pan-Pacific Surgical Association. At this time, the separate entity of the axillary segment of the upper lobe was accepted but, to conform with the modern terminology, this segment was given the term lateral. So also the segments of the middle lobe were given the terms lateral and anterior. The subapical segment was accepted as a separate division of the lower lobe but the term lateral basal was given to the axillary basal segment.

Illustrations are given to enhance the authors' conviction that all human lungs are not cast in one identical mold but show variations in anatomical make-up which should be borne in mind. They stress the satisfaction they have experienced in using the Moolten method of fixing lungs to demonstrate the bronchopulmonary segments; subsequent inflation results in sharp and lasting delineation of the segments. The disadvantages of other methods of demonstration are overcome and the specimen thus prepared makes a graphic impression on the observer and may be used for years.

HILDING.

ESOPHAGUS

Congenital Strictures of the Esophagus, with Diverticula of the Esophagus.

Wildenberg, V. D.: *Les Annales d'Oto-laryngologie* 65:390-397 (July) 1948.

Five cases are presented of congenital strictures of the esophagus, seen in infants. The cause is unknown. There were sac-like dilations above the esophageal strictures. There was severe vomiting, suggestion of pyloric stenosis, and loss of weight. X-ray pictures taken after swallowing a barium sulfate suspension revealed the contours of the dilated and strictured esophagus. Three of the infants were all in one family. Four of the cases were cured by repeated dilatations by means of a bougie passed through the esophagoscope. The fifth infant died, following a laparotomy.

The author advocates repeated dilatations with a bougie passed through an esophagoscope. No description of the bougie is given.

HARKINS.

Considerations in the Surgical Treatment of the Complications in Cases of Foreign Bodies in the Esophagus.

Lugli, P.: *Les Annales d'Oto-laryngologie* 66:85-92 (Mar.) 1949.

The author presents the subject of foreign bodies in the esophagus which are not possible to remove with the esophagoscope. These are the cases of large, or sharp and irregular objects, which either have traumatized the esophageal walls or have actually perforated. Early and prompt external incision in the neck is advised. The neck is opened along the anterior border of the sternocleidomastoid muscle and the esophagus exposed. The foreign body is removed, either through an incision in the wall of the esophagus, or, if it has already perforated, from the peri-esophageal tissues. If an abscess is present it is drained externally.

Four cases are presented, one of a foreign body within the esophagus, two cases where the foreign body had perforated, and one of an esophageal fistula resulting from an external wound.

HARKINS.

Notices

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The American Board of Otolaryngology will conduct the following examinations in 1950:

January 8-11 in New Orleans, Louisiana, at the Hotel St. Charles.

May 17-20 in San Francisco, California, at the Hotel Mark Hopkins.

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The National Committee for Chile is now receiving gifts for the library of the medical school of the University of Chile at its new collection center in the Library of Congress, Washington. The newer materials in the library, including periodicals, books and reference materials, were totally destroyed in the recent fire. Medical periodicals of the last ten years and recent medical books are urgently needed. Your contribution will be appreciated.

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**HEARING AIDS ACCEPTED BY THE
COUNCIL ON PHYSICAL MEDICINE AND REHABILITATION
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(List Corrected to December 1, 1949)

Aurex (Semi-Portable)	Radioear Permo-Magnetic
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